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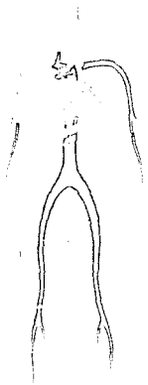

NEUROPHYSIOLOGICAL RESPONSES TO STRESSFUL MOTION AND ANTI-MOTION SICKNESS DRUGS AS MEDIATED BY THE LIMBIC SYSTEM

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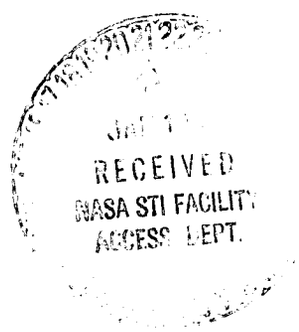

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NEUROPHYSIOLOGICAL RESPONSES TO STRESSFUL MOTION AND ANTI-MOTION SICKNESS DRUGS AS MEDIATED BY THE LIMBIC SYSTEM

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Neurophysiological Responses to Stressful Motion and Anti-Motion Sickness Drugs as Mediated by the Limbic System

by

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ABSTRACT (TECHNICAL)

This report has characterized performance in terms of attention and memory, categorizing extrinsic mechanisms mediated by ACTH, norepinephrine and dopamine, and intrinsic mechanisms as cholinergic. The cholinergic role in memory and performance has been viewed from within the limbic system and related to volitional influences of frontal cortical afferents and behavioral responses of hypothalamic and reticular system efferents. The inhibitory influence of the hippocampus on the autonomic and hormonal responses mediated through the hypothalamus, pituitary, and brain stem are correlated with the actions of such anti-motion sickness drugs as scopolamine and amphetamine. These drugs appear to exert their effects on motion sickness symptomatology through diverse though synergistic neurochemical mechanisms involving the septohippocampal pathway and other limbic system structures. The particular impact of the limbic system on an animal's behavioral and hormonal responses to stress is influenced by ACTH, cortisol, scopolamine, and amphetamine. These agents share a number of neurochemical actions which can be regarded as neurophysiologically equivalent, differing mainly in a temporal sense and in terms of the scope of their metabolic influence.

A neurophysiologically defined neural mismatch theory is defined that integrates preceding discussion on memory, attention, stress, the neurochemistry of anti-motion sickness drugs, performance behavior and the limbic system. A parallel is drawn between the ability of scopolamine and stress hormones to modulate attention, reinforcement, memory and the psychological stress of neural mismatch that leads to motion sickness. Essentially, neural mismatch is characterized as a process by which ongoing sensory experience is associated with a neural store of reality that cannot be satisfactorily reconciled or habituated, thus causing excessive psychological stress and eventual sickness and vomiting. Drugs like scopolamine which interfere with memory and learning are conceptualized to exert part of their therapeutic action through disruption of necessary associative mechanisms of learning and memory. Without the association of present sensory experience with past experience, the psychological impact of the neural mismatch is not as readily appreciated or channeled into a stress response.

Summarizing, drugs like scopolamine may be of therapeutic benefit to motion sickness because of sedative or hypnotic properties through which conscious awareness of stressful novelty is subjectively impaired. Manipulation of the body's stress hormone system may instead be therapeutically valuable due to an enhancement of adaptive capabilities that allow novelty to be recognized with greater perspective. This occurs without the disorientation and sickness that attends excessive efforts at neural mismatch in intensely novel environments. The value of pharmacological manipulation of the stress hormone system can not be overemphasized in our quest to prophylactically treat motion sickness, after all, this system is designed to serve an adaptive role in stress situations in the first place.

ABSTRACT (LAYMAN'S)

Man's performance is dependent upon his ability to attend to and remember environmental events as well as maintenance of a continuous connection between long-term memory and ongoing sensory experience. It is through this association that he is able to make meaningful judgements about the significance or survival impact of familiar and novel environmental occurrences. Neurons located within the brain in a region known as the limbic system have been shown to be important in the memory process. Those neurons which release a neurochemical known as acetylcholine are particularly important in short-term memory and in the establishment of long-term memory. The anti-motion sickness drugs scopolamine and amphetamine are able to block the transmission mediated by these neurons. Consequently, they impair short- and long-term memory and associative processes. Neurons in the limbic system also influence the activity of neural centers in the hypothalamus which regulate the release of stress hormones like adrenal corticotropic hormone (ACTH) and cortisol.

The neurochemical processes that result in motion sickness are partially blocked by drugs like scopolamine and amphetamine. This report has established a relationship between the anti-motion sickness properties of these drugs and the ability of these drugs to interfere with processes of memory, learning, and the control of stress hormones released by the hypothalamus.

The definition of neural mismatch in unambiguous terms has been undertaken as well. Neural mismatch has been hypothesized to occur when ongoing sensory experience is associated with long-term memory such that the two experiences are found to be grossly discordant. This imposes an adaptive pressure or stress on the system that can eventually lead to sickness. Sickness is a normal response mechanism to discordant sensory experience, especially when a number of sensory systems are involved and when few other sensory systems can be identified as functioning properly. Therefore, in a zero-gravity environment, when so many of the major senses are in conflict, the vomiting response occurs as part of an evolutionary mechanism that may normally have evolved to evacuate poisons from the gastrointestinal system. The main inference of this report is that this vomiting mechanism is initiated as a result of the association of ongoing sensory experience with long-term memory and is mediated through the limbic system.

Drugs like scopolamine block the association of ongoing sensory experience with long-term memory and thus block the generation of a neural mismatch. The implicit assumption in this argument is that the ability to retain short-term memory experiences is necessary before any significant comparison can be made between established reality and moment to moment novelty. Alternatively, one might hypothesize that mechanisms of attention and reiteration within the limbic system are necessary to maintain a focus upon the contrast between short- and long-term memory, a process which also establishes new memory.

Because zero-gravity is a stressful novelty, it follows that the hormonal responses to microgravity or any other stress are normal adaptative mechanisms designed to enable the animal to survive in the new environment. It furthermore stands to reason that these hormones should initiate metabolic and neurochemical events appropriate to this end. A number of these neurochemical events have been identified and described in detail by this report. This reasoning and the association of the actions of these hormones with the pharmacology of the anti-motion sickness drugs clearly underscores the immense value and need for further research in this area.

PREFACE

The problems of space motion sickness are related to the inadequacy of present predictive and preventative methodologies. Although pharmacological intervention is most effective at present, the utility of this approach is confounded by intolerable side-effects. The most effective drugs and drug combinations, namely scopolamine, scopolamine-dexedrine, and promethazine-ephedrine, are not taken at the appropriate times pre-launch, but instead are administered after orbital insertion. While this approach eliminates the possibility of debilitating side effects during critical launch periods, it also severely compromises the effectiveness of the medications in controlling motion sickness. Because the issue of performance decrement is fundamental to the proper use of present medications, the authors undertook a literature search with the intent of defining the nature and extent of the effects of these drugs and motion sickness on performance. This information was envisioned as supplementary to present efforts to develop ground-based, quantitative measures of performance so that individual astronaut candidates and subject populations could be evaluated in terms of their responses to particular medications or general motion sickness.

The literature search that was undertaken with the intent of defining the nature and extent of the effects of these medications and motion sickness on performance resulted in the generation of this report on the neurophysiological responses of the limbic system to stressful motion and anti-motion sickness drugs. This was a natural consequence of the discovery of the role of the limbic system in memory, learning, extinction, and sensory discrimination; all key components in the evaluation of an individual's ability to perform.

TABLE OF CONTENTS

I. INTRODUCTION

This report discusses performance, memory, learning, extinction, discrimination, reactions to novelty, sensory input, and sensory thresholds all within the context of a functioning limbic system. It reveals how scopolamine, amphetamine, and stress hormones influence the functions carried out by the limbic system and provides further clues to the mechanisms of action of our more effective anti-motion sickness drugs. Finally, the experimental evidence is summarized through the advancement of a neurophysiologically defined neural mismatch theory of motion sickness. The limbic system is postulated to embody most of the central mechanisms and processes that are necessary in the recognition of a neural mismatch and essential to the elicitation of motion sickness symptomatology based upon this recognition. Neural mismatch itself is defined in broader terms which allows the inclusion of more experimental findings and the integration of different lines of evidence from such fields as neurophysiology, neurochemistry, neuroanatomy, neuropharmacology, the behavioral sciences, and pharmacology. This particular description of neural mismatch is regarded as a major objective and finding of this literature search and fills an important gap in our understanding of motion sickness in physiological terms that are precisely defined. The limbic system theory of motion sickness, as it pertains to older, more established conceptualizations such as sensory conflict or neural mismatch must still be regarded as a heuristic hypothesis, yet one which presently is best able to account for the majority of the experimental findings available.

Figure 1 depicts a flowchart which traces the various lines of inquiry underscoring the development of this neurophysiologically defined neural

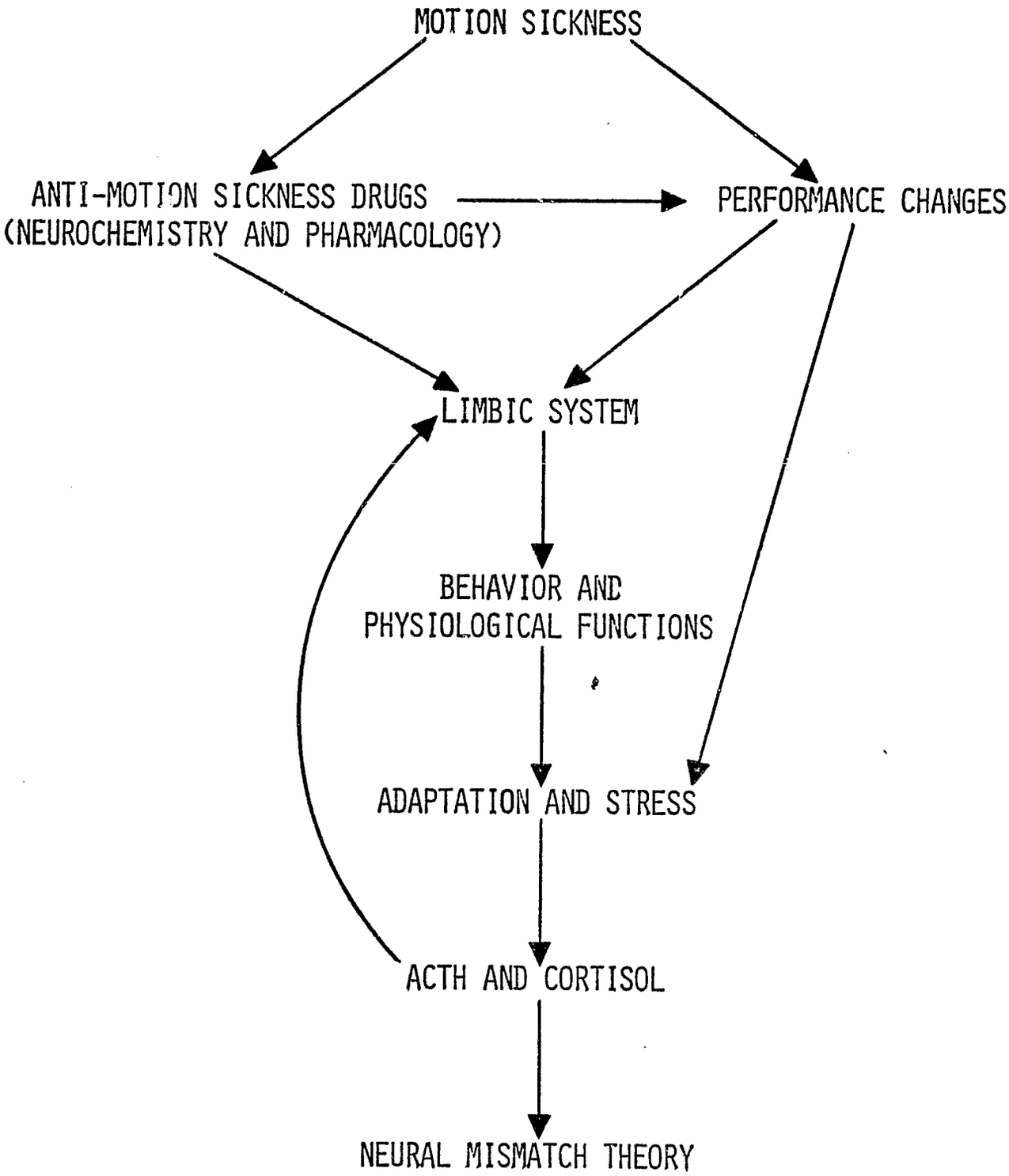


Fig. 1

mismatch theory in the etiology of motion sickness, or more simply put, the limbic system theory of motion sickness. The flowchart also clearly indicates the reasoning behind the advocation of the testing of stress hormones (ACTH and cortisol) for prevention of motion sickness, which will be described in detail in this report.

The phenomenon of motion sickness (see Figure 1) has empirically led to the discovery of a number of pharmacological agents that, while effective in the prevention or treatment of motion sickness, are derived from notably diverse classes of drugs. Scopolamine (a cholinolytic), amphetamine (a sympathomimetic) and promethazine (an antihistaminergic and anticholinergic), for instance, are perhaps the best known and most effective drug agents available. Furthermore, there are data that indicates that changes in performance occur as a result of motion sickness or medication with anti-motion sickness drugs. It is not at all surprising that a relationship exists between motion sickness and performance. The fact that the neurochemical and neurophysiological actions of these individual drugs have been well studied in their own respect suggests logically that the identification of the sites of action of these drugs might provide clues to new brain regions and mechanisms which are critically involved in the expression of motion sickness and hence, the processes underlying the disorder. The search for these critical regions is facilitated in part by the desirability of finding regions in which different classes of anti-motion sickness drugs exert therapeutic or pharmacologic actions and where those actions are neurochemically or neurophysiologically equivalent. Although it is not necessary that this condition be met, because of the possible involvement of more than one region in the malady, those areas responsive to all drugs are more attractive. The

septohippocampal pathway of the limbic system and the medial vestibular nucleus are identified as regions in which both scopolamine and amphetamine moderate impulse transmission. The limbic system, however, is the only region identified so far and by this report that can account for the behavioral changes that follow anti-motion sickness drug administration. It also plays an easily recognizable role in the expression of the symptomatology of motion sickness.

Having established the limbic system as a possible candidate or participant in neural mechanisms underlying or modulating motion sickness, further investigation of the behavioral and physiological functions of the limbic system demonstrate the important role of this region in adaptive responses to environmental stress. The region is found to specifically concentrate the stress hormones, ACTH and cortisol, and to be responsive to physiological changes in their levels. Preliminary data from the Neurophysiology and Biomedical Laboratories at the Johnson Space Center furthermore suggest that pituitary-adrenal-cortical hormones may modulate motion sickness susceptibility. The data obtained raises the possibility that those individuals with high ACTH levels are less susceptible to stressful motion. This report presents the necessary background allowing interpretation of the significance of this finding.

Finally, the limbic system is described in terms which indicate its suitability as a model for the neural mismatch theory of motion sickness. The actions of our more effective anti-motion sickness drugs on the limbic system are recognized and interpreted as consistent with this model. Furthermore, the precise neurophysiological functions of the limbic system, including its

relationship to the hypothalamus, autonomic nervous system and pituitary gland, is highly indicative of the importance of this brain region in the expression of the symptomatology of motion sickness.

Considering the size and diversity of the scientific information that is available in each of these fields, it is the plan of this writing to organize the background material into specific sections. Each section is discussed thoroughly and written to allow that section to be understood without requiring extensive understanding of other sections. While this approach tends to make each section more comprehensible, the reiteration of material within a number of sections cannot be avoided and, in fact, tends to highlight the more important background materials in this report. Major sections include: 1) Memory and Performance, 2) Limbic Systems, 3) Stress, 4) Neurotransmission and Anti-Motion Sickness Drugs, 5) The Hypothalamico-Pituitary-Adrenal Axis, and 6) Neural Mismatch Theory.

II. MEMORY AND PERFORMANCE

A. DEFINITIONS

The wider the range of a drug's effect on behavior, the less its usefulness. It is of primary importance to understand whether a change in performance reflects a change in memory storage, a change in a biologically significant system that influences memory, or a change unrelated to memory that appears only because the drug under study affects a particular measure of performance (136). Scopolamine and amphetamine are examples of drugs that exert a wide range of effects on behavior. This lack of specificity derives largely from the fact that both scopolamine and amphetamine are particularly potent drugs that act on neurotransmitter systems subserving diverse functional roles in the central nervous system (CNS).

Principal concepts that have guided neurobiological investigations of memory include a distinction between intrinsic and extrinsic neural systems, the concept of modulation, a distinction between short-term and long-term storage mechanisms, and the concept of consolidation. The distinction between intrinsic and extrinsic systems comes from cellular investigations of learning and memory in invertebrates. The intrinsic system refers to pathways where representations of information develop, presumably as a result of alterations in synaptic efficacy; the extrinsic system refers to pathways that can influence the development, maintenance, or expression of memory, but which do not themselves contain the memory. For example, consider the case of habituation of gill withdrawal in the invertebrate Aplysia, in which memory

develops as synaptic changes occur along the same pathways that are hard-wired for performance of the response (136).

The idea of an extrinsic system, which developed from invertebrate neurobiology, gives meaning to the related concept of modulation. Functions such as attention, reward, and arousal will necessarily influence memory as we ordinarily speak of it and must be regarded as modulatory influences. The concept of consolidation has a broader interpretation. Some refer to consolidation as the process by which resistance to disruption develops gradually after training. Consolidation, by this usage, involves long-term memory and can continue for years. Others refer to consolidation as the relatively short-lived process of transition from a labile short-term storage system to a viable long-term storage system, knowing that the time period after training during which memory can be disrupted need not reveal the time course of consolidation (136).

B. ROLE OF THE CHOLINERGIC SYSTEM

Extensive literature on the effects of drugs that alter the efficacy of brain acetylcholine (ACh) suggests that cholinergic synapses may be part of the intrinsic system that accomplishes memory storage. The results of a number of experimental findings show that memory storage involves, in part, a sequence of changes in efficacy at cholinergic synapses that develops with time after learning (31). Specifically, for a task that can be remembered for weeks, these changes are thought to involve first a gradual increase in efficacy of cholinergic transmission for several days after learning, and then a gradual decrease in efficacy during the course of forgetting. One partic-

ularly interesting drug that affects the cholinergic system is physostigmine; an acetylcholinesterase inhibitor that has been observed to influence memory. However, on closer examination it has been learned that the effects of physostigmine treatment depend not only on drug dose and age of the memory, but also on the efficiency of original learning. Specifically, during the days after learning, slow learners responded to physostigmine differently than fast learners. It has been suggested that the hypothesized sequence of synaptic changes subserving memory storage occur more rapidly for the fast learners, so that this group achieves the stage of retention that can be disrupted by physostigmine sooner than slow learners. Taken together, the evidence strongly suggests that synaptic changes occur gradually after learning and their time course is related to the natural lifetime of the memory. Because effects of these drugs can apparently be obtained throughout the lifetime of a memory, and because these effects reveal properties of the memory storage process, it seems reasonable to localize these hypothetical synaptic changes to the intrinsic system, i.e., to the ensemble of neurons actually storing information.

If the intrinsic system for information storage involves the same neuronal systems required for performing the task that is to be remembered, then it follows that cholinergic drugs should not produce pure amnesia but instead should produce a state of cognitive impairment that includes amnesia. This expectation seems borne out by studies of adult humans (38,40) and monkeys (7) showing that scopolamine produces a broad impairment in cognitive functions including memory, which resembles the pattern of cognitive deficits observed in aging.

Despite this convergence of supporting data, the idea that cholinergic synapses store memory, still rests on indirect evidence. Techniques are not yet available to determine directly either the synaptic basis of long-term memory storage or the neurotransmitters involved. It remains possible that cholinergic drugs are exerting their effects via cholinergic neurons upon crucial noncholinergic systems.

Studies of the effects of cholinergic blockers such as scopolamine in man (24,25,40,47,48,66,82,104) and in experimental animals (11) have revealed that scopolamine effects acquisition of new information; that is, short-term memory, but does not influence retrieval or long-term memory. Drugs which facilitate cholinergic transmission, such as arecholine, choline and physostigmine, are effective in enhancing learning in individuals that are not already task-proficient. Hence, poor learners and average chess players are benefited whereas good performers and expert chess players (and probably highly trained astronauts) are not benefited or actually experience performance decrements (76,134). These findings gain intuitive meaning when one considers the analogous situation in which alertness, stimulants, and depressant drugs are examined. Specifically, a stimulant will increase the alertness of a dosing individual, but is more likely to confuse and disorient an already wide-awake individual.

The effects of separate treatment with lecithin or choline have also been examined. Seven early-stage Alzheimer patients received daily incrementing doses of lecithin for four weeks, reaching an average dose of approximately 75 g per day (44). Three of the patients improved their scores in a test of new learning ability without changes in immediate memory, remote memory, or other

cognitive skills. Choline (9 g daily for 21 days) improved memory test performance to a small extent in three patients identified as exhibiting early-stage Alzheimer's disease, but did not affect th. test scores of patient's with more advanced stages of the disease (130). Presumably, late-stage Alzheimer's disease involves the extensive loss of cholinergic neurons which by their absence would preclude any beneficial response to choline. Finally, three other studies of choline involving 3 to 18 patients found no changes in mental status following one to two months of daily choline treatment (8 g to 15 g) (45,113,120). Taken together, the available studies have been largely disappointing. The small number of patients studied, lax experimental designs, inadequate attention to dosage, and the lumping together of results from early-stage and late-stage patients have made it difficult to draw any firm conclusions about the possible usefulness of cholinergic drugs in dementia.

More information is known about the effects of cholinergic drugs in normal adult subjects. Infusions of arecholine (4 mg) (134) or physostigmine (1.0 mg/hr) (29) facilitated greater word learning in poor learners. Arecholine (i.v. 2 mg) also facilitated word recall when the drug was given immediately after learning (143). A single oral dose of choline (10 g) improved serial learning in normal subjects (133). All these effects were small but reliable. Regimens of cholinergic drugs given over longer periods of time have been less effective. Thus, choline chloride (16 g/day for 2 days) had no effect on memory test scores in normal elderly subjects (89), and no effect was observed in normal young adults, when the same dose was given for a three-day period (28).

In summarizing these data, it is useful to keep in mind the elegant animal studies that first demonstrated that the effects of cholinergic drugs are largely determined by drug dose and by the age of the memory. Efforts to develop therapeutically useful applications of this work will no doubt be constrained by these two variables.

C. ACTH AND ATTENTION

The whole molecule $ACTH_{1-39}$ or the fragment $ACTH_{4-10}$ increases resistance to extinction of aversively or appetitively motivated tasks. That is, it prolongs performance of a previously acquired behavior after reinforcement has been withdrawn (16,34). Initial acquisition of the same task need not be affected by ACTH treatment (52,58). Second, ACTH or ACTH fragments can restore the impaired acquisition of shock-avoidance learning exhibited by hypophysectomized animals (32). Given prior to retention testing these same substances can reportedly attenuate the retrograde amnesia caused by CO_2 or electro-convulsive shock (117). These particular effects of ACTH are believed to be independent of its classical endocrine action on the adrenal glands primarily because $ACTH_{4-10}$, which is virtually devoid of adrenocortical activity, exerts these same effects (42,56).

Resistance to extinction has been analyzed carefully in other contexts (80). Changes in attention, arousal, or motivation can underlie variations in extinction rate. It is unclear whether this phenomenon should be taken as evidence that a drug exerts effects on memory. Moreover, it is widely recognized that whenever a drug is active during behavioral testing, it is difficult to separate effects on memory from effects on other aspects of brain

function, and to exclude possibly trivial effects. For example, changes in shock sensitivity or locomotor activity can markedly affect the performance measure in some tasks (84).

The finding that the restorative effects of ACTH on acquisition performance of hypophysectomized animals are short-lived (15,64) suggests that ACTH may not be influencing learning and memory, since effects on memory might be expected to endure beyond the acquisition phase. Similarly, the so-called anti-amnesic actions of ACTH and ACTH fragments are consistent with effects on arousal or on learning ability and without further analysis cannot be taken as evidence for improved memory.

The available studies on human subjects given ACTH fragments are in agreement with the animal studies in that these substances do not seem to exert any direct effect on memory. This conclusion is based on failures to observe effects on memory in double-blind, controlled studies of normal volunteers given single infusions of 15-30 mg of $ACTH_{4-10}$ prior to tests of free recall (122), paired associate learning (36,124) and short-term retention of verbal or nonverbal material (87,120). ACTH-like peptides, however, do seem to affect performance on some tasks requiring detection or vigilance. These effects have been taken to reflect improvement in attentional processes.

Hormones like ACTH are thought to mediate some of the physiological consequences of an experience. Brain events initiated by the action of such hormones are though to influence whether information about an experience will be remembered. Thus, the role of ACTH is considered to be modulatory; its action on memory storage occurs via an extrinsic system that operates after

information has been registered. This influences whether information should enter long-term storage.

In contrast to ACTH, vasopressin's effects on behavior appear to be relatively long-lasting. When given after training lysine-vasopressin (LVP) prolonged extinction for at least three days (33). Similarly, when given daily for seven days (1 mg/day subcutaneously) arginine-vasopressin (AVP) improved shuttlebox avoidance learning of hypophysectomized rats and maintained performance at a stable level for up to seven days after the test injection (15). Post-training administration of AVP or LVP, facilitated long-term retention of passive avoidance training (1,17,49,72) and long-term retention of sexually motivated learning (14).

D. AMPHETAMINE AND THE BIOGENIC AMINES

Pretraining or post-training electrolytic lesions of the locus coeruleus, which can reduce norepinephrine (NE) by 60-80% in cortex and hippocampus, does not appear to affect retention (3,71,118,151,152). In the case of dopamine (DA), lesions of substantia nigra, which can reduce striatal DA to about 5% of normal levels (105), did not disrupt passive avoidance acquisition or retention. The evidence indicates that learning and memory can often proceed normally in the presence of combined or separate depletion of brain NE and DA. Brain NE levels might relate primarily to the stress associated with training or to the degree of arousal produced by a noxious stimulus. In this sense brain NE levels after passive avoidance training may vary with the specific training and treatment conditions, reflecting the familiar rule that performance is best at an optimal level of arousal.

A group of studies has shown that the facilitatory effect of post-training amphetamine on retention (84) is probably due to peripheral effects of amphetamine. This is because intraperitoneal but not intraventricular injection of amphetamine heightened retention (78). Furthermore, dl-4-OH-amphetamine, a drug that primarily affects peripheral catecholamines, facilitated retention (79). Lastly, the effects of both 4-OH-amphetamine and d-amphetamine on memory were blocked by adrenal demedullation (79). A role for epinephrine in memory is therefore likely. The possibility that learning and memory in humans might be improved under some circumstances has been explored using drugs that affect catecholamines. It is well known that stimulants such as amphetamine and caffeine can improve performance on a variety of tasks, particularly ones that are boring and fatiguing for normal subjects. However, these drugs do not appear to be particularly effective for tasks that require concentrated intellectual effort (144) such as those tasks performed by astronauts. Studies of amphetamine and methylphenidate on learning and memory have involved learning-disabled children, healthy aged subjects, depressed patients, and normal adults. Facilitatory effects have been obtained most reliably in subjects presumed to be functioning suboptimally or in young children, whose information-processing capacity has not yet fully matured. Thus, 20 mg of d-amphetamine improved word recall in depressed patients (1651).

It has been suggested that the arousal state of the animal interacts with a given dose of stimulant drug to determine performance. Facilitation of performance occurs when the level of arousal associated with training is inadequate and the drug can promote an optimal level of arousal. By this

view, facilitation of retention should be difficult to obtain in healthy, optimally functioning astronauts and the general population.

Neurophysiological studies of the locus coeruleus, the major source of forebrain NE, have shown that this structure can exert modulatory influences on sensory input (149). The disruption of short-term memory by scopolamine is more pronounced during periods of sensory stimulation as if competing neural activity were competing with rehearsal mechanisms necessary for retention (135). In addition, post-training lesions of locus coeruleus do not disrupt retention (151,152). Taken together, these considerations emphasize the possible involvement of catecholaminergic systems at the time of information input - in attention, organization of new motor programs, and other forms of information analysis - rather than in post-training, gradually developing processes required for the consolidation of enduring memory.

E. SCOPOLAMINE AND SHORT-TERM MEMORY

A number of earlier investigations of the effects of scopolamine on performance have overlooked its influence on the particular measures used in assessing performance. Learning and memory tests are often dependent upon accurate visual discrimination and yet the effects of scopolamine on visual accommodation and discrimination are often neglected in interpretation of the results (61). Some studies in monkeys have been performed that were not confounded by inaccurate visual discrimination and which concluded that disruption of short-term memory by scopolamine is more pronounced over longer retention intervals (up to 10 seconds) than after zero second retention (8).

This implies that the memory of the experience is fleeting and that learning of the memory trace is blocked.

The fact that the decrement of both memory and cognitive function by scopolamine can be reversed by physostigmine but not by amphetamine or methylphenidate argues further that cholinergic transmission is specific to memory processes (6,38). Because depletion of norepinephrine impairs the process of memory retrieval but without any loss of the original memory (59), it follows that NE is most likely operating through the extrinsic system. Scopolamine impairs memory for tactile, optical, acoustic, and auditory stimuli. In addition, it impairs performance I.Q. in man (104) in tests that were designed to overcome the effects that impaired attentional processes would have on the acquisition of new information. Although the subjects were well motivated, they still had great difficulty concentrating on the task. Other investigators have likened the cognitive deficits produced by scopolamine to aging in which attentiveness is impaired (38,40).

Deficits of human memory may involve impairment of a cholinergic component in the hippocampus as indicated by the measurement of a loss of hippocampal cholinergic enzymes as well as studies employing the cholinergic blocking drug scopolamine (109). Severe memory loss has been well documented in man after lesions of the hippocampus (39,41,104). Newly trained rats demonstrate a clear elevation of ACh content in the hippocampus with smaller changes noted in cortex (81). Furthermore, animals that have been characterized as having good retention ability also have higher rates of choline uptake and conversion to ACh in the hippocampus (110). Alzheimer's disease which is often referred to as senile dementia, is characterized by a decreased level of

ACh in the neocortex and by reduced levels of choline acetyltransferase, the enzyme that synthesizes ACh, in neocortex and hippocampus (116). Hereditary or experimentally induced decrement of choline acetyltransferase-specific activity weakens both long-term retention and the facilitatory effect of post-trial stimulation on learning and yet paradoxically improves short-term retention (65).

F. MEMORY AND PERFORMANCE - LAYMAN'S SUMMARY

The data are consistent with a view of memory whereby information storage occurs through alterations in connectivity along neural pathways already specialized for different kinds of information processing. These intrinsic, information-containing neural ensembles are not fully established at the moment of learning, but develop and change with time in a way that reflects their modulation by extrinsic systems. Extrinsic systems, for example, might signal the significance of previously occurring events by providing information about their consequences. Cholinergic drugs appear unique in their ability to influence memory of a particular event throughout the lifetime of the memory. Accordingly, these drugs seem best understood as affecting synaptic substrates of information storage. Other substances (e.g., vasopressin, ACTH, NE, and DA), which are most effective shortly after learning, seem best understood as exerting modulatory effects on memory. Furthermore, the putative effects of these substances on arousal, fear and attention raise the possibility that modulation reflects specific and different influences on memory, rather than some single influence.

III-LIMBIC SYSTEMS

A. ANATOMY AND PHYSIOLOGY

1. Introduction

This chapter describes the structure and function of the limbic system. Special attention is afforded to those components of the limbic system which are influenced by anti-motion sickness drugs like scopolamine and amphetamine, and by stress hormones like cortisol and ACTH. All of the figures and a portion of the descriptive text accompanying these figures have been taken from a recent text entitled "The Human Central Nervous System" (97).

Certain territories of the diencephalon, the telencephalon and the mesencephalon are structurally and functionally so closely interrelated that they may be considered a single functional complex, which has been designated as the limbic system. This system is represented at the diencephalic level by the hypothalamus. Its telencephalic components include the preoptic and septal regions, the hippocampus, some adjacent cortical areas, and the amygdala. The midbrain area of the limbic system is formed by a number of cell masses all of which lie in or close to the median plane. Figure 2 presents the various moieties of the limbic system and their fiber connections in an extremely schematised fashion.

The hypothalamus encompasses the most ventral part of the diencephalon (Fig. 3). Caudally the hypothalamus passes gradually over into the periven-

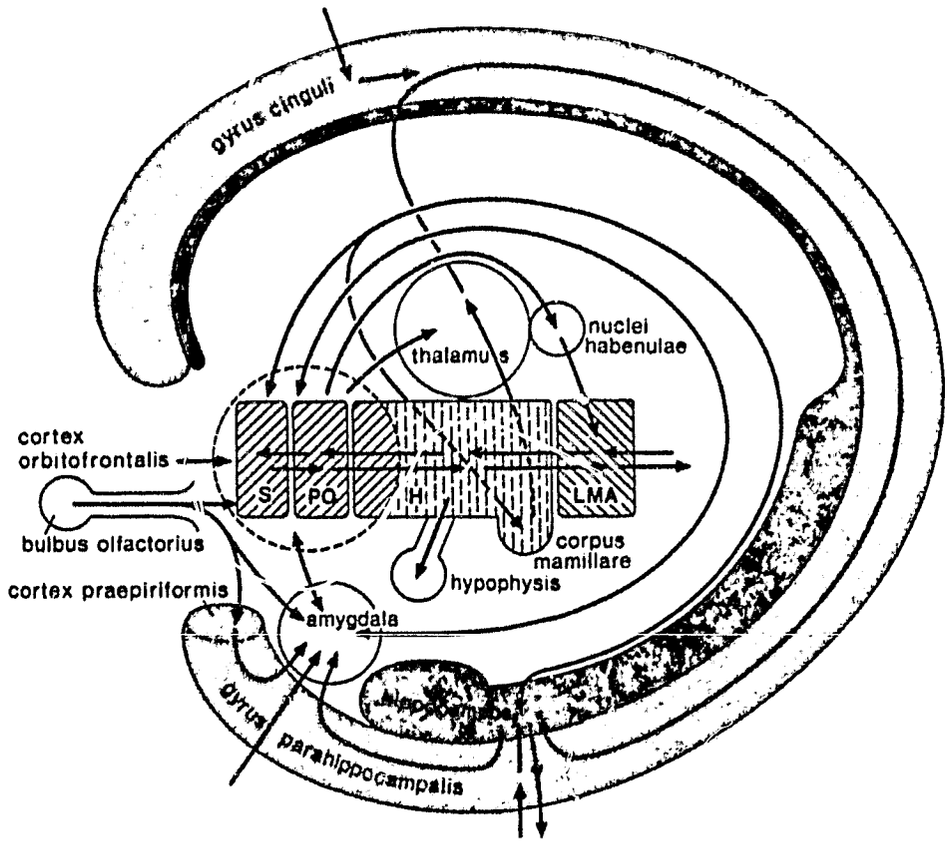
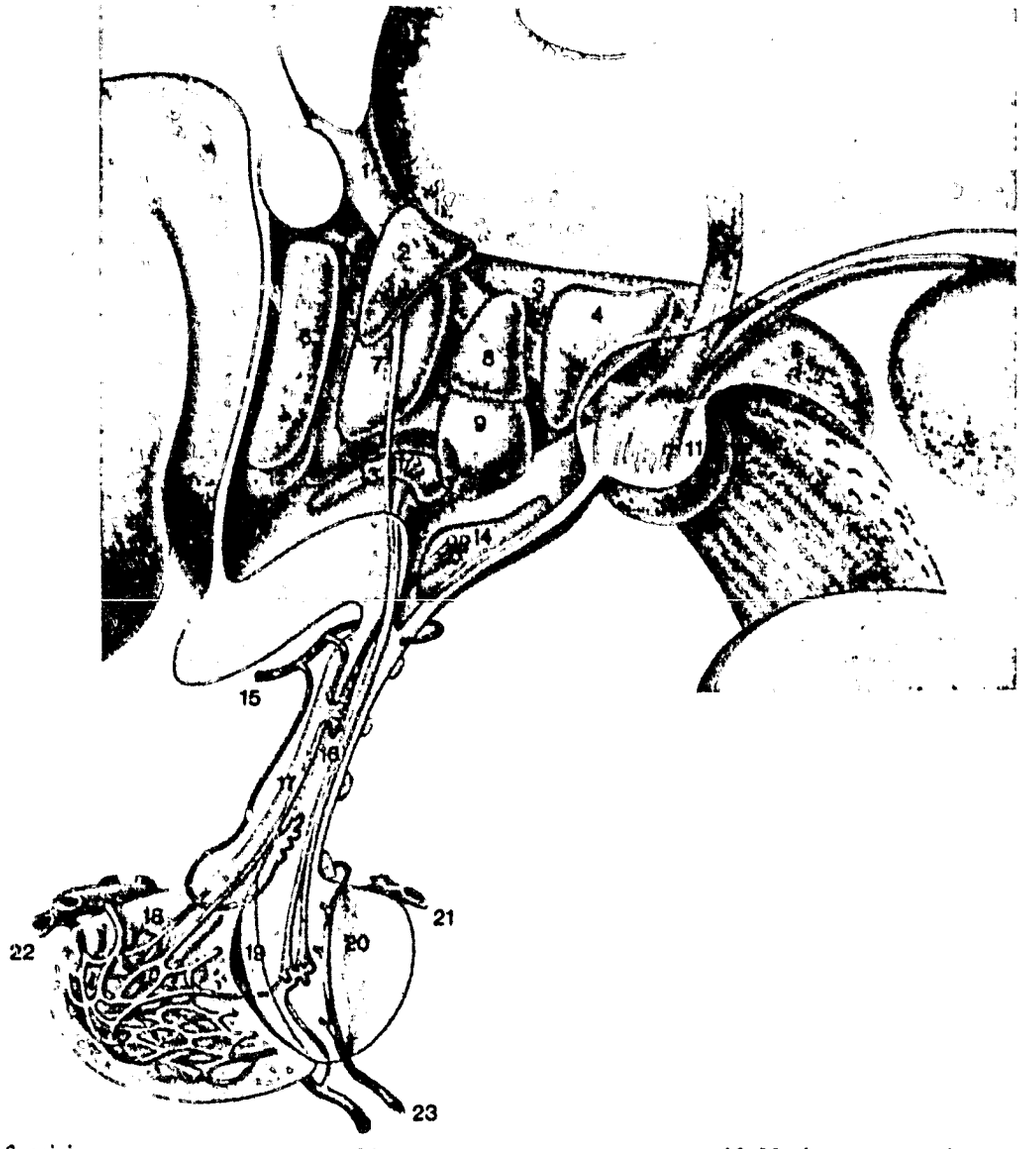


Fig. 2 Summary of the limbicohypothalamic complex. Subdivision of the area into central units and limbic rings. *H*, hypothalamus; *LMA*, limbic midbrain area; *PO*, preoptic region; *S*, septum



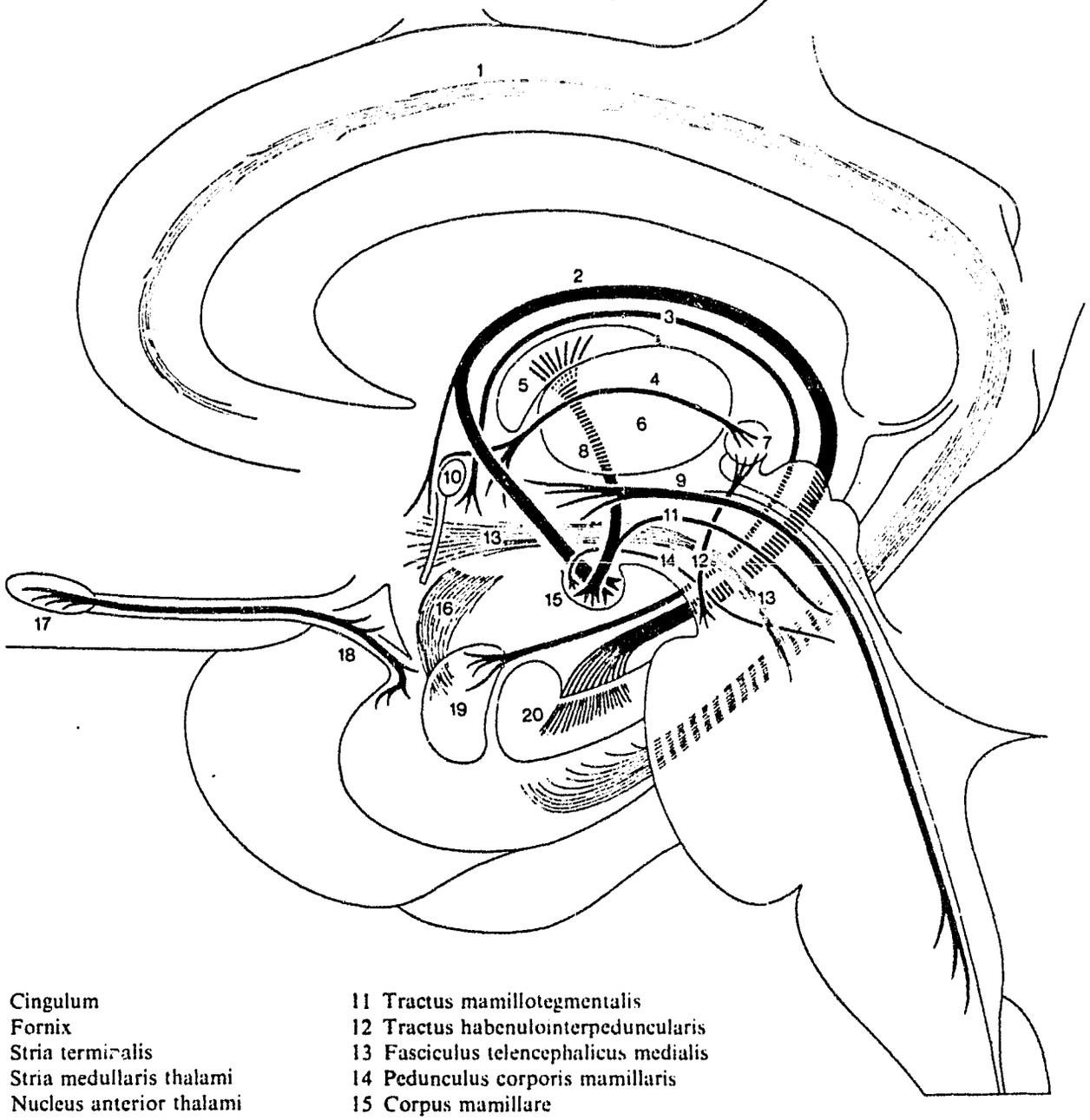
1 Columna fornicis
2 Nucleus paraventricularis
3 Area lateralis hypothalami
4 Nucleus posterior hypothalami
5 Area tegmentalis ventralis
6 Nucleus praeopticus medialis
7 Nucleus anterior hypothalami
8 Nucleus dorsomedialis
9 Nucleus ventromedialis
10 Fasciculus mamillaris princeps
11 Corpus mamillare
12 Nucleus praeopticus lateralis
13 Nucleus supraopticus
14 Nucleus infundibularis
15 Arteria hypophyseos superior dextra
16 Infundibulum
17 Pars infundibularis } Lobus anterior
18 Pars distalis } hypophyseos
19 Pars intermedia
20 Lobus posterior hypohyseos
21 Sinus intercavernosus posterior
22 Sinus intercavernosus anterior
23 Arteria hypophyseos inferior sinistra
24 Arteria hypophyseos inferior dextra

Fig. 3 The hypothalamic nuclei and the relationship between the hypothalamus and the pituitary gland (4/1 ×)

tricular and tegmental grey of the mesencephalon. It is, however, customary to define the posterior margin of the hypothalamus as a vertical plane passing just caudal to the mammillary bodies. The infundibular stalk, which is situated directly posterior to the optic chiasm, connects the funnel-shaped rostroventral part of the hypothalamus with the pituitary gland. The lateral hypothalamic zone is partly separated from the medial zone by the postcommissural fornix, a large bundle connecting the hippocampal formation with the mammillary bodies (Figs. 3 and 4).

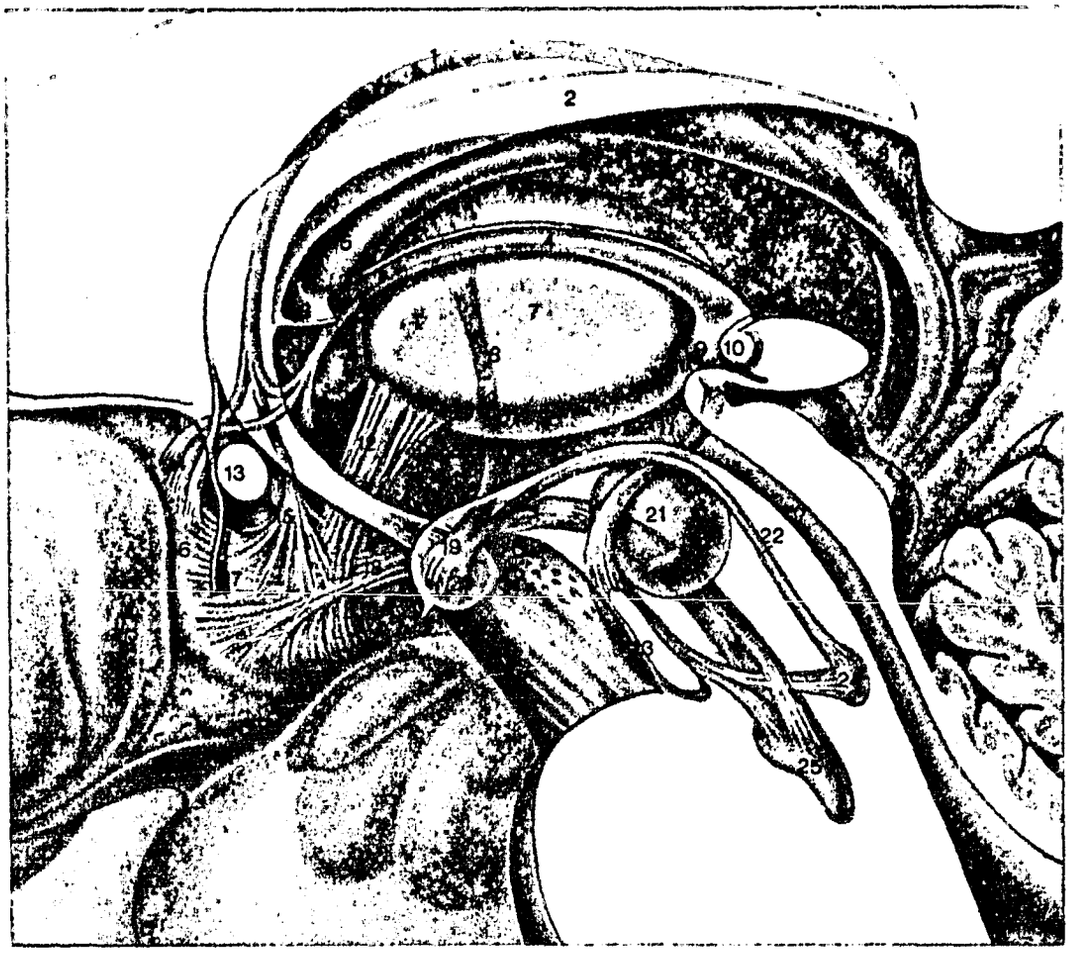
The preoptic region is of telencephalic origin, and is closely related structurally to the hypothalamus. The septal region borders on the nucleus accumbens septi, a large cell mass that in location and function occupies a position intermediate between the limbic and striatal or extrapyramidal systems. The septal region is well developed in the human brain. The so-called limbic midbrain area (Fig. 5) encompasses the regions in the lower right corner of the figure but also includes the dorsal raphe nucleus.

Taken together these fibers constitute one large functional system, which has been designated as the "limbic system-midbrain circuit". Schematising somewhat it may be stated that the septal, preoptic, and anterior hypothalamic areas form the rostral pole of this circuit, whereas the paramedian midbrain area represents its caudal pole. The hypothalamus may be characterised as a nodal way station interposed between these rostral and caudal poles. Two large telencephalic parts of the limbic system, namely the amygdala and the hippocampal formation, as well as the olfactory system are reciprocally connected with the rostral pole of the circuit (Figs. 2 and 4). The caudal pole of the circuit may be considered as a paramedian subdivision of the brain



1 Cingulum
2 Fornix
3 Stria terminalis
4 Stria medullaris thalami
5 Nucleus anterior thalami
6 Nucleus medialis thalami
7 Nuclei habenulae
8 Tractus mamillothalamicus
9 Fasciculus longitudinalis dorsalis
10 Commissura anterior
11 Tractus mamillotegmentalis
12 Tractus habenulointerpeduncularis
13 Fasciculus telencephalicus medialis
14 Pedunculus corporis mamillaris
15 Corpus mamillare
16 Ansa peduncularis
17 Bulbus olfactorius
18 Stria olfactoria lateralis
19 Corpus amygdaloideum
20 Hippocampus

Fig. 4 The major pathways of the limbic system and the rhinencephalon



1 Stria terminalis
2 Fornix
3 Commissura fornicis
4 Stria medullaris thalami
5 Nucleus anterior thalami
6 Tela choroidea ventriculi tertii
7 Nucleus medialis thalami
8 Tractus mamillothalamicus
9 Nuclei habenulae
10 Commissura habenulae
11 Tractus habenulointerpeduncularis
12 Pedunculus thalami inferior
13 Commissura anterior
14 Precommissural components of { stria terminalis / stria medullaris thalami / fornix }
15 Stria terminalis postcommissuralis
16 Septum verum
17 Lamina terminalis
18 Fasciculus telencephalicus medialis
19 Fasciculus mamillaris princeps
20 Corpus mamillare
21 Nucleus ruber
22 Tractus mamillotegmentalis
23 Nucleus interpeduncularis
24 Nucleus tegmentalis dorsalis
25 Nucleus centralis superior

Fig. 5 The central part of the limbic area; medial view of nuclei and tracts (5/2 ×)

stem reticular formation. The centers forming this pole are to a large extent integrated into both ascending and descending pathways. The ascending pathways connect the lower parts of the reticular formation and the visceral sensory centers situated in the caudal part of the medulla oblongata with the hypothalamus. The descending pathways convey impulses from the hypothalamus to the visceral and somatic motor centers in the brain stem and spinal cord. These descending pathways are particularly important in that they probably mediate the production of motion sickness symptomatology including, changes in heart rate, respiration, temperature, sweat, nausea, and vomiting.

2. Hypothalamus

Focussing now on the hypothalamus, it should be emphasized that this center, apart from its bidirectional linkages with the various parts of the limbic forebrain-midbrain continuum, entertains several other important functional connections. The following four may be mentioned:

(1) The lateral preoptico-hypothalamic zone is reciprocally connected with the medial and certain midline nuclei of the dorsal thalamus. The nucleus parafascicularis is one of the midline nuclei of particular interest in this report (see later) because of its special function in the behavioral effects and binding of ACTH. The midline nuclei are also unique in their diffuse projection to all areas of the cerebral cortex.

(2) The lateral preoptico-hypothalamic zone receives a direct input from the orbitofrontal part of the neocortex. This input from the frontal cortex may embody volitional influences on the limbic system. Impulses from this

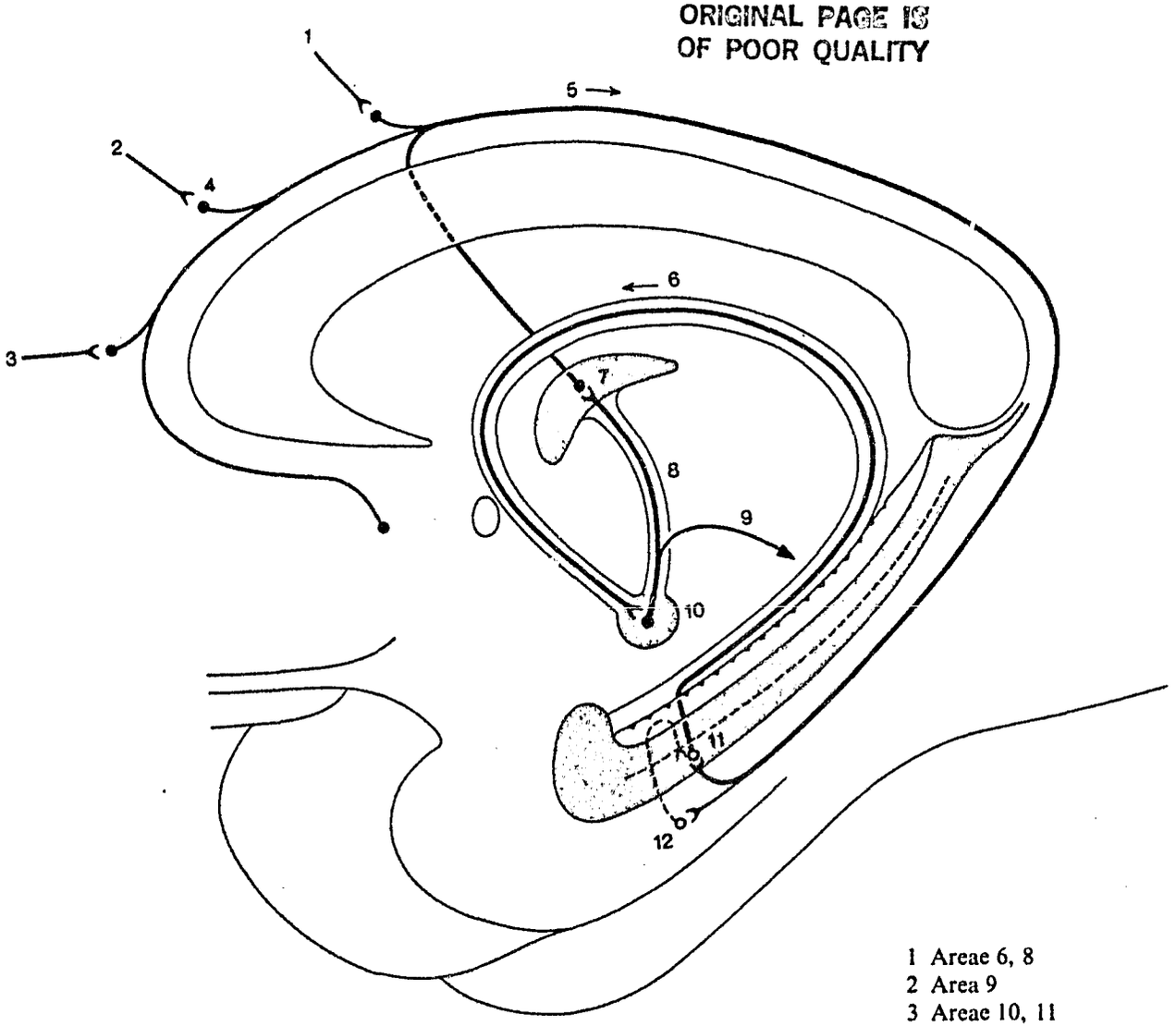
cortical region probably mediate the conscious experience of motion sickness and zero-gravity thus representing the psychological components of the experience.

(3) The mammillary body, which is situated in the caudobasal part of the hypothalamus, receives a large projection from the hippocampal formation and sends most of its efferents to the anterior nucleus of the thalamus. These two connections form part of a closed hippocampo-mammillo-thalamo-cingulo-hippocampal system known as the circuit of Papez (Figs. 4 and 6).

(4) The effector mechanism of the hypothalamus includes, apart from fiber systems descending to the brain stem and spinal cord, two hypothalamo-hypophyseal pathways. By way of one of these, the partly neural and partly humoral tubero-infundibulo-hypophyseal system, the hypothalamus controls the production of the various hormones of the anterior pituitary (Fig. 3) (37). This particular aspect of hypothalamic function will be discussed at length in subsequent chapters dealing with stress and the hypothalamic-pituitary-adrenal axis.

3. Physiological Functions

The limbic system is known as the visceral brain because it is functionally associated with emotional aspects of behavior related to survival of the individual and the species, together with visceral responses accompanying these emotions, and the brain mechanism for memory. The visceral responses to activity within the limbic system are mediated mainly through the hypothalamus and include changes in respiration, gastrointestinal movements



1 Areae 6, 8
2 Area 9
3 Areae 10, 11
4 Area 24
5 Cingulum
6 Fornix
7 Nucleus anterior thalami
8 Tractus mamillothalamicus
9 Tractus mamillotegmentalis
10 Corpus mamillare
11 Subiculum
12 Area 28

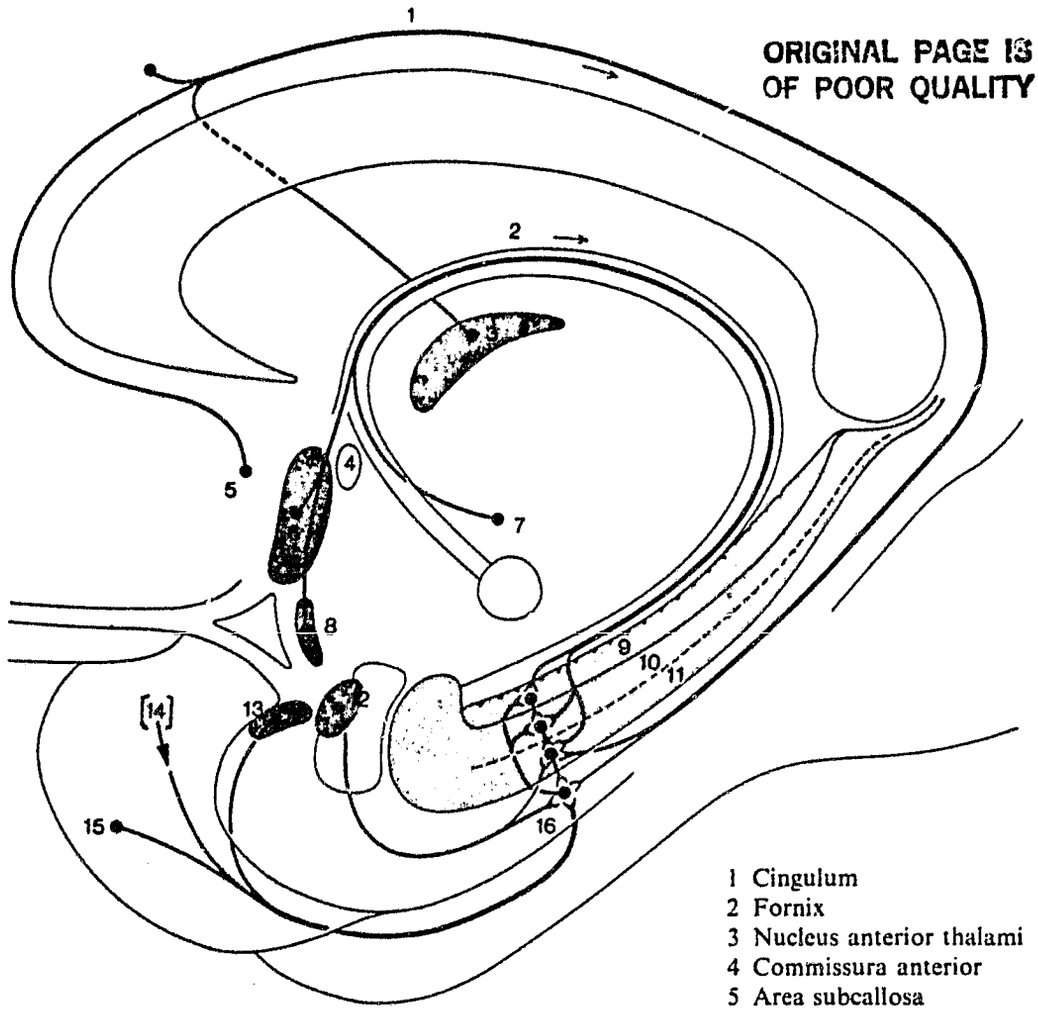
Fig. 6. The circuit of Papez

and secretion, piloerection, and pupillary dilation. Understanding of neurophysiologic regulation of visceral functions is primary to elucidation of the neural components of motion sickness and the neuropharmacological bases of anti-motion sickness drug therapy. Behavior associated with survival of the species; that is, adaptive responses of the organism to novel or changing environments, may be closely tied to memory and new learning. Furthermore, the visceral responses accompanying adjustment to novel environments may include the vomiting response whenever the organism's perception of the sensory world is dramatically changed such as by the ingestion of some poisonous or hallucinogenic plant product.

Money (91) has proposed that emesis is a natural response to sensory mismatch. He hypothesizes that this mismatch occurs during motion sickness, while contending that the underlying survival-related mechanism is part of a response mechanism to poison. The possibility that the limbic system is intimately associated with these behavioral functions is highly likely. Further aspects of the limbic system will be discussed below.

4. Hippocampus

The hippocampus or hippocampal formation is a large C-shaped structure that forms part of the medial wall of the cerebral hemisphere. The retrocomissural hippocampus is well developed and represents the main portion of the hippocampal formation. It constitutes the archipallial part of the cerebral hemisphere and contains a relatively simple three-layered allocortex throughout its extent. The fascia dentata is laterally continuous with the cornu ammonis, which in turn passes over into the subiculum (Fig. 7). The



1 Cingulum
2 Fornix
3 Nucleus anterior thalami
4 Commissura anterior
5 Area subcallosa
6 Nuclei septi
7 Hypothalamus
8 Nucleus gyri diagonalis
9 Fascia dentata
10 Cornu ammonis } Hippocampus
11 Subiculum
12 Nuclei corticalis + medialis amygdalae
13 Cortex praepiriformis
14 Cortex frontalis
15 Cortex temporalis
16 Gyrus parahippocampalis

Fig. 7 Afferents of the hippocampus

fascia dentata contains a granule cell layer of small neurons, whereas large, pyramidal elements prevail in both the cornu ammonis and the subiculum. The subicular cortex is contiguous with the juxtallocortex or mesocortex. The latter represents a type of cortex that is transitional between the hippocampal allocortex and the neocortex. This transitional cortex covers the parahippocampal gyrus and is also found in the supracallosal cingulate gyrus. The hippocampus, the parahippocampal gyrus and the cingulate gyrus constitute a large arcuate convolution known as the limbic lobe. The allocortical hippocampus forms the inner ring, whereas the mesocortical parahippocampal and cingulate gyri form the outer ring of that lobe (Fig. 2)

The hippocampus receives afferent fibers from: (1) the area entorhinalis, (2) the septum, (3) the hypothalamus, and (4) the rostral brainstem (Fig. 7). These connections may be documented as follows:

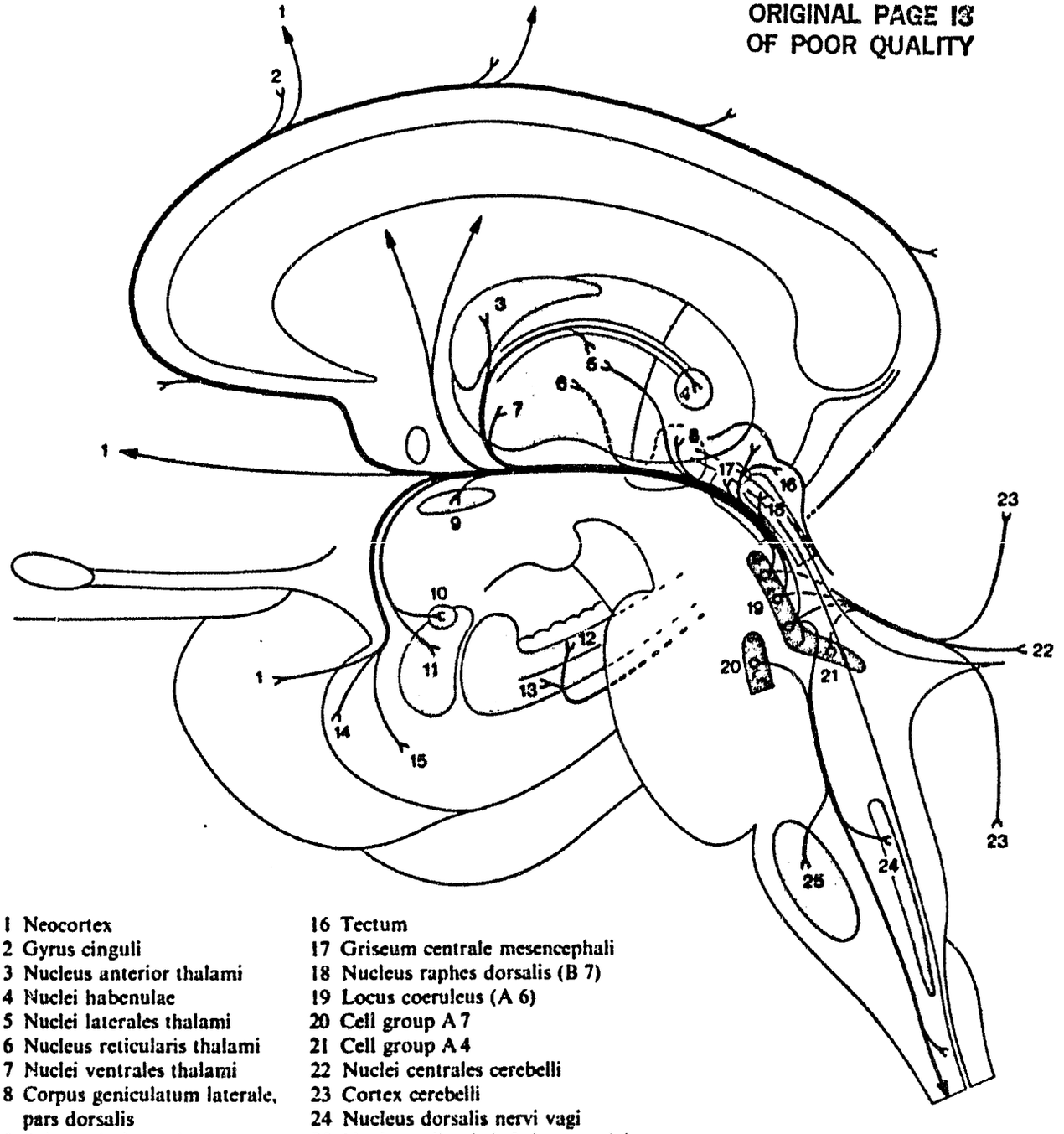
(1) The most conspicious and quantitatively most important input to the hippocampus is formed by afferents from the area entorhinalis. The fibers terminate in the fascia dentata as well as in the cornu ammonis. The entorhinal area, in its turn, receives a large projection from the subiculum as well as from the cornu ammonis and is also in communication with other widespread areas of the cerebral cortex. Subcortical afferents of the entorhinal area include a large projection from the anterior thalamic nucleus which, like the cingulate fibers, passes through the cingulum.

(2) The medial septal nucleus sends fibers by way of the fornix to the cornu ammonis and the subiculum.

(3) In the rat the hippocampus receives a direct input from the dorsal raphe nucleus, and the locus coeruleus. Several of these connections have been demonstrated to contain monoaminergic fibers (Figs. 8 and 9).

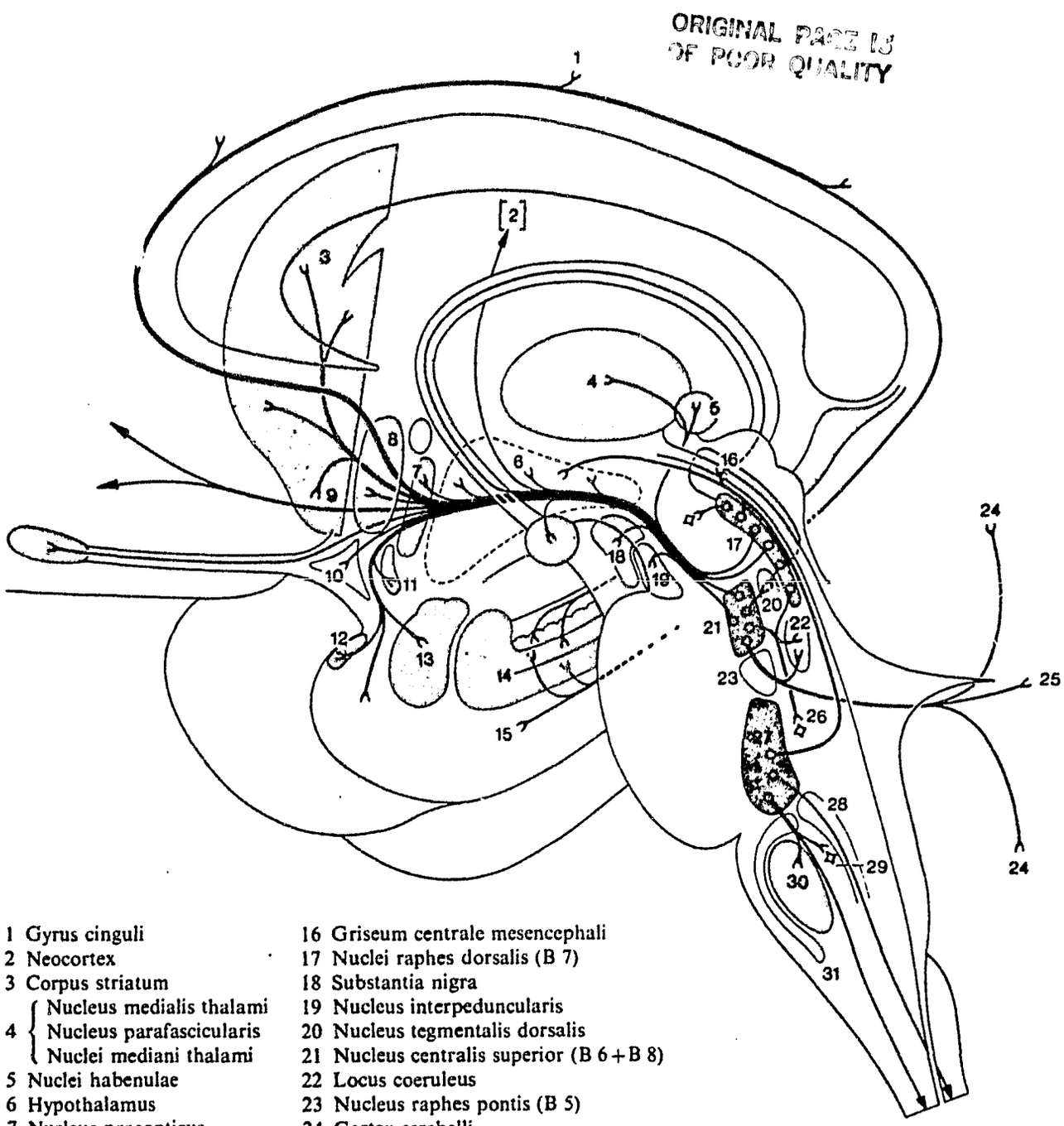
The axons of the dentate granule cells terminate in a highly ordered manner within the cornu ammonis; the latter sends fibers to the subiculum (Fig. 7). These connections presumably constitute a directionally polarized, sequential pathway, whereby input to the hippocampus passes successively through the fascia dentata and cornu ammonis to the subiculum where, as has been recently established, the majority of all hippocampal efferents, both cortical and subcortical, originate.

Describing the hippocampal formation in less precise but more meaningful terms, one might regard the hippocampal formation as a conduit through which conscious experience reaches and influences centers controlling autonomic, emotional and instinctual processes. Memory, and therefore learning, is definitely dependent upon an intact limbic system. It can be conjectured that the highly circular and positive feedback circuits contained within the limbic system, such as the circuit of Papez (Fig. 6), reinforce or maintain a conscious perception at the cortical level as long as the associative and integrative centers contained within the frontal lobes signal the significance of that associative process. Provided that these associative processes are continued, the entrainment of new memory (i.e., learning) occurs along with the elicitation of any behavioral, hormonal or autonomic actions that are appropriate. For example, the novel sensory experience of zero-gravity traces its pattern across the cerebral cortex, is perceived through associative processes as a survival-stress that cannot be reconcilliated or habituated by



1 Neocortex
2 Gyrus cinguli
3 Nucleus anterior thalami
4 Nuclei habenulae
5 Nuclei laterales thalami
6 Nucleus reticularis thalami
7 Nuclei ventrales thalami
8 Corpus geniculatum laterale, pars dorsalis
9 Substantia innominata
10 Nucleus centralis amygdalae
11 Nuclei basalis + lateralis amygdalae
12 Cornu ammonis
13 Subiculum
14 Cortex piriformis
15 Cortex entorhinalis
16 Tectum
17 Griseum centrale mesencephali
18 Nucleus raphes dorsalis (B 7)
19 Locus coeruleus (A 6)
20 Cell group A 7
21 Cell group A 4
22 Nuclei centrales cerebelli
23 Cortex cerebelli
24 Nucleus dorsalis nervi vagi
25 Nucleus olivaris inferior + nuclei olivares accessorii

Fig. 8 The noradrenergic system I: connections of the locus coeruleus



1 Gyrus cinguli
2 Neocortex
3 Corpus striatum
4 { Nucleus medialis thalami / Nucleus parafascicularis / Nuclei mediani thalami
5 Nuclei habenulae
6 Hypothalamus
7 Nucleus praeopticus
8 Nuclei septi
9 Nucleus accumbens
10 Tuberculum olfactorium
11 Nucleus gyri diagonalis
12 Cortex praepiriformis
13 Corpus amygdaloideum
14 Hippocampus
15 Cortex entorhinalis
16 Griseum centrale mesencephali
17 Nuclei raphes dorsalis (B 7)
18 Substantia nigra
19 Nucleus interpeduncularis
20 Nucleus tegmentalis dorsalis
21 Nucleus centralis superior (B 6+B 8)
22 Locus coeruleus
23 Nucleus raphes pontis (B 5)
24 Cortex cerebelli
25 Nuclei centrales cerebelli
26 Formatio reticularis pontis
27 Nucleus raphes magnus (B 3)
28 Nucleus raphes obscurus (B 2)
29 Formatio reticularis myelencephali
30 Nucleus olivaris inferior + nuclei olivares accessorii
31 Nucleus raphes pallidus (B 1)

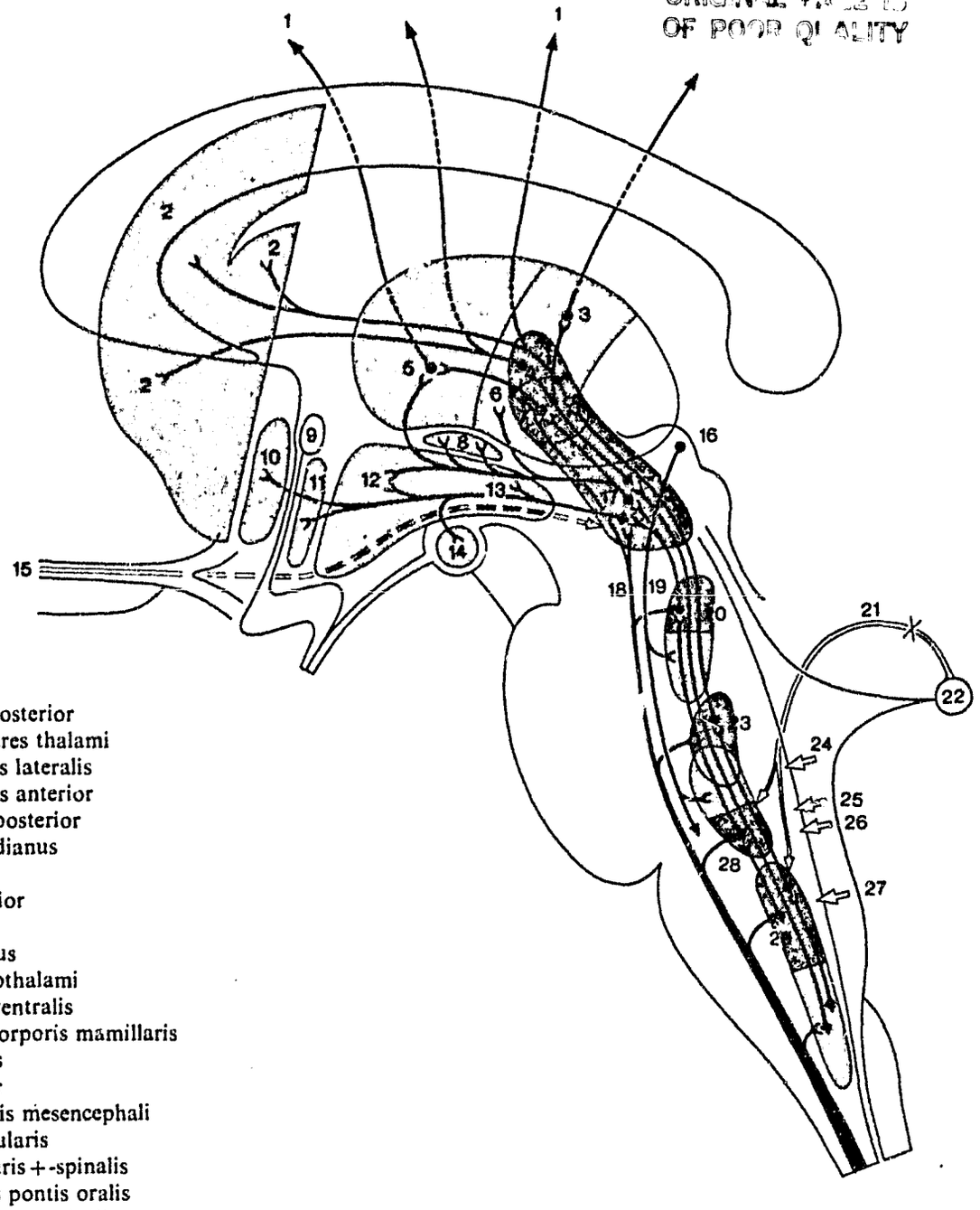
Fig. 9 The serotonergic system

conventional means and which manifests itself through diverse sensory modalities. Finally, the sustained adaptive pressures exerted in large part through the influence of the frontal cortex on the hippocampus, hypothalamus, pituitary, and reticular formation result in the systemic sickness characterized as motion sickness. The continual release distribution and accumulation of neurotransmitters, their metabolites, and other compounds may be factors in causing this sytemic sickness.

5. Reticular Formation

It is clear that the level of arousal of an animal or man is important in determining if extensive attention will be afforded to any conscious perception including the perception of zero-gravity. It is known that the general population and astronauts do not get sick when asleep and that drugs like promethazine and scopolamine induce drowsiness and impair short-term memory. Amphetamine, although it stimulates the cortex and elicits stereotypic locomotor behavior, still impairs limbic system function, an action not necessarily fully appreciated at a conscious level. It is important to understand how the reticular system stimulates the limbic system because there is evidence that anti-motion sickness drugs may impair the ability of this system to alert or activate cortical and limbic structures.

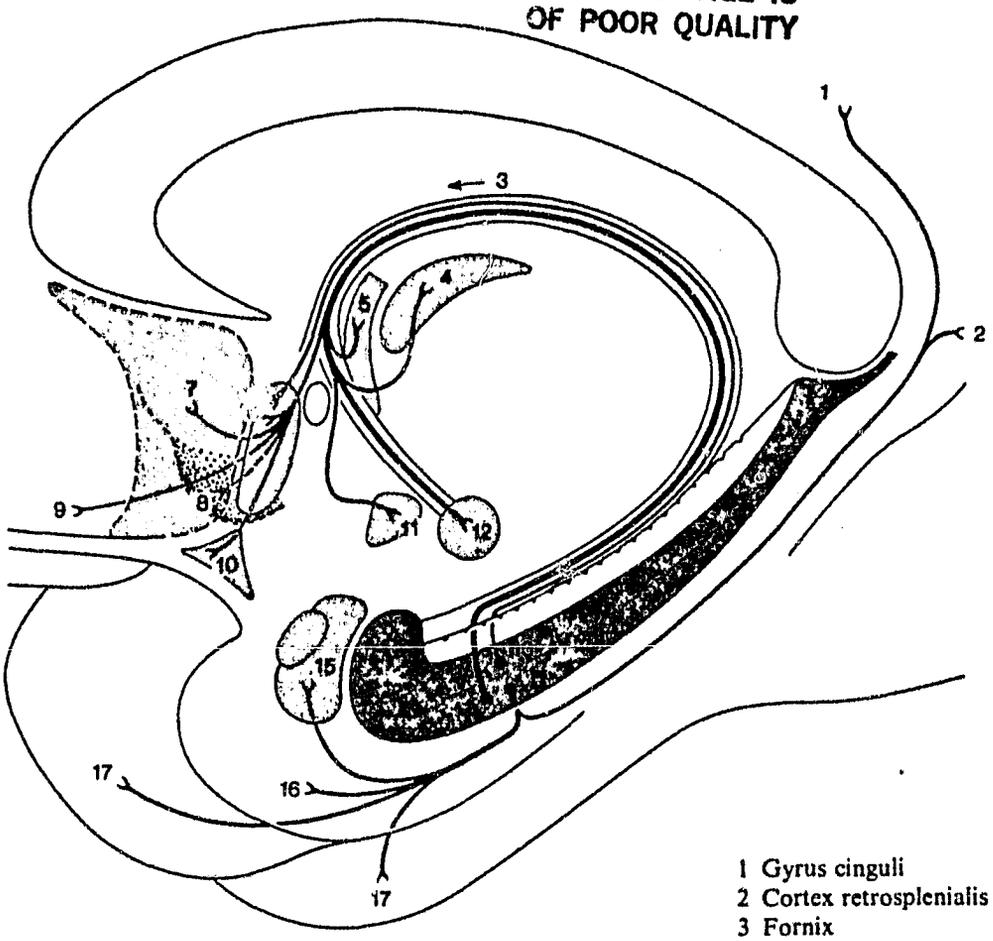
Electrocortical arousal by reticular stimulation of hippocampectomized cats is difficult and, unlike the arousal obtained in normal animals, lasts only for the duration of the stimulus. Figure 10 depicts the ascending fiber systems of the reticular formation; revealing the pathways through which vestibular input is registered (#26) and the limbic system structures



1 Neocortex
2 Corpus striatum
3 Nucleus lateralis posterior
4 Nuclei intralaminares thalami
5 { Nucleus ventralis lateralis / Nucleus ventralis anterior }
6 Nucleus ventralis posterior
7 Nucleus centromedianus
8 Zona incerta
9 Commissura anterior
10 Nuclei septi
11 Nucleus praeopticus
12 Area lateralis hypothalami
13 Area tegmentalis ventralis
14 Nucleus lateralis corporis mamillaris
15 Tractus olfactorius
16 Colliculus superior
17 Formatio reticularis mesencephali
18 Tractus spinoreticularis
19 Tractus tectobulbaris+-spinalis
20 Nucleus reticularis pontis oralis
21 Fasciculus uncinatus cerebelli
22 Nucleus fastigii
23 Nucleus reticularis pontis caudalis
24 Trigeminal input
25 Acoustic input
26 Vestibular input
27 Solitarian input
28 Nucleus gigantocellularis
29 Nucleus medullae oblongatae centralis

Fig. 10 Ascending fibre systems of the reticular formation

receiving input from the reticular formation (#10, 11, 12, 13 and 14). It is likely that these hippocampal effects are achieved by influences acting on some part of the brain external to the hippocampus, rather than as an intrinsic property of the hippocampus itself (75). Stimulation of the reticular formation leads to the production of the theta-rhythm (or regular slow-wave activity, RSA) characteristic of the limbic system (148). The frequency of this rhythm is proportional to the intensity of stimulation; lower frequencies are associated with behavioral reactions to novelty or frustrative non-reward whereas higher frequencies indicate initiation of performance of learned behavioral patterns (13,85). Sensory stimuli generally initiate these theta waves, most likely through stimulation of the reticular formation. Theta waves represent arousal reactions of the hippocampus and are behaviorally analogous to desynchronization or arousal of the cortical EEG which also follows stimulation of the reticular formation (21). During the theta-rhythm both pyramidal and granule cells increase their firing in phase with the rhythm. Input to these hippocampal and dentate cells from cholinergic neurons located in the medial septal nuclei (Fig. 7) is necessary for the rhythm. Drugs which block cholinergic transmission, such as scopolamine or atropine, attenuate the theta-rhythm (22) and prevent sensory-induced desynchronization of the neocortex. Although superficially both nicotine and muscarinic agonists induce an alert EEG, their effects differ in several important aspects. Nicotinic arousal of the EEG may depend on the intactness of the reticular formation, as compared with the more diffuse arousal of the EEG caused by muscarinic agonists (35,57). A major output from the hippocampus (Figs. 4, 6 and 11) passes directly through a relay in the mammillary body to the anterior thalamus which connects directly with medial cortex or, through links with the ascending cholinergic reticular



1 Gyrus cinguli
2 Cortex retrosplenialis
3 Fornix
4 Nucleus anterior thalami
5 Bed nucleus of stria terminalis
6 Nucleus septi lateralis
7 Cortex frontalis medialis
8 Nucleus accumbens
9 Gyrus rectus
10 Nucleus olfactorius anterior
11 Nucleus ventromedialis
12 Corpus mamillare
13 Cornu ammonis
14 Subiculum
15 Corpus amygdaloideum
16 Cortex entorhinalis
17 Cortex temporalis

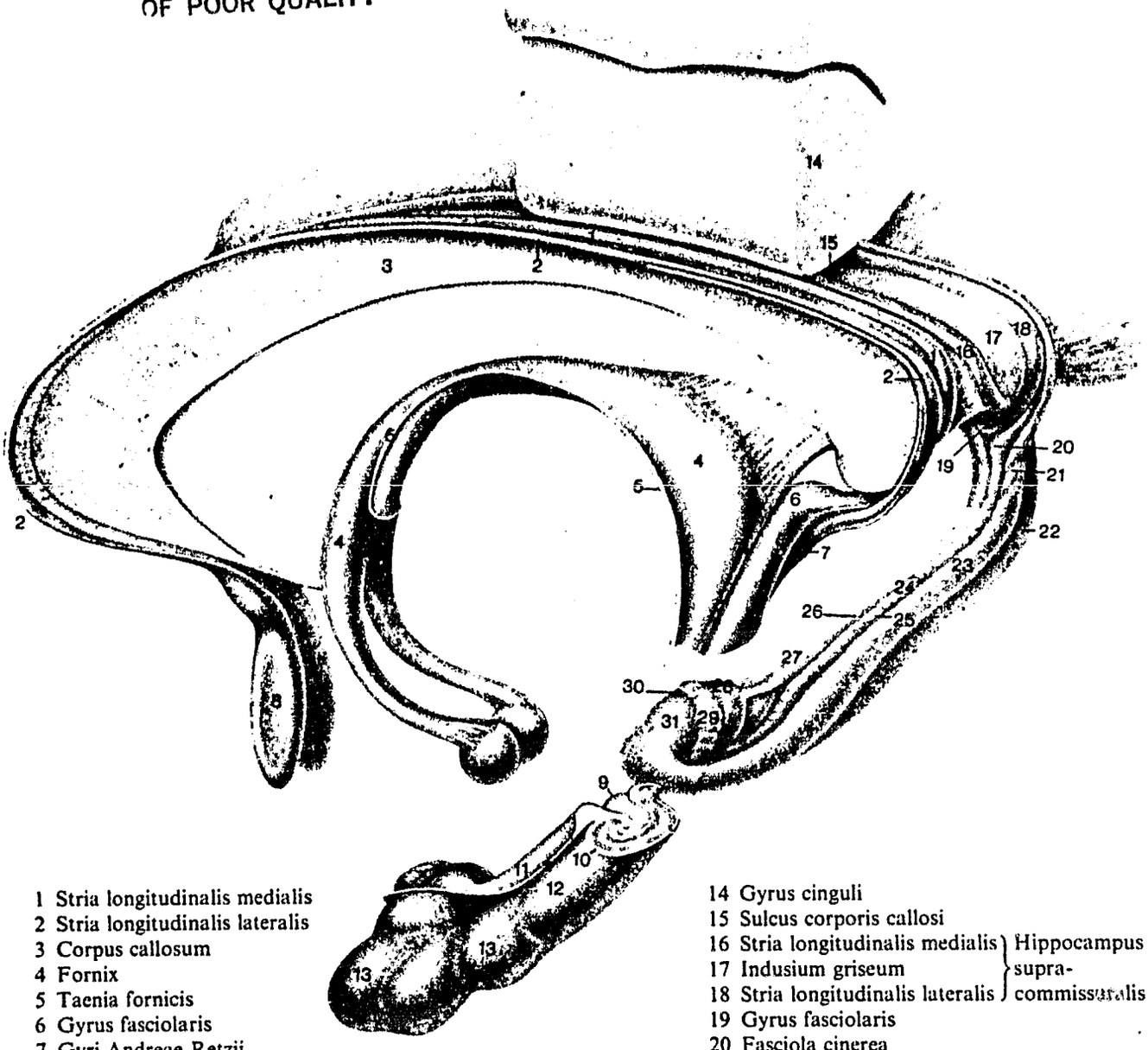
Fig. 11 Efferents of the hippocampus

system, with the lateral cortex of the cerebral hemispheres (22,30,69,75,107). Additional linkage is made directly with the entorhinal, temporal and frontal cortex as well (Fig. 11). Thus, the limbic system may be critical to maintaining alertness.

6. Fornix

Further understanding of the fornix is warranted because of the importance of the cholinergic septo-hippocampal pathway which runs with the fibers of the fornix and because of the influence of anti-motion sickness drugs on impulse conduction through these fibers and the neurochemistry of the septum and hippocampus. Considerable investigation of the behavioral effects of lesions of the fornix has been undertaken and in large part demonstrates that lesions of the fornix mimick the pharmacological effects of scopolamine. Considering the efferent connections of the hippocampus, it should be stated that the entire postcommissural fornix and a considerable part of the precommissural fornix originate from the subiculum rather than from the cornu ammonis.

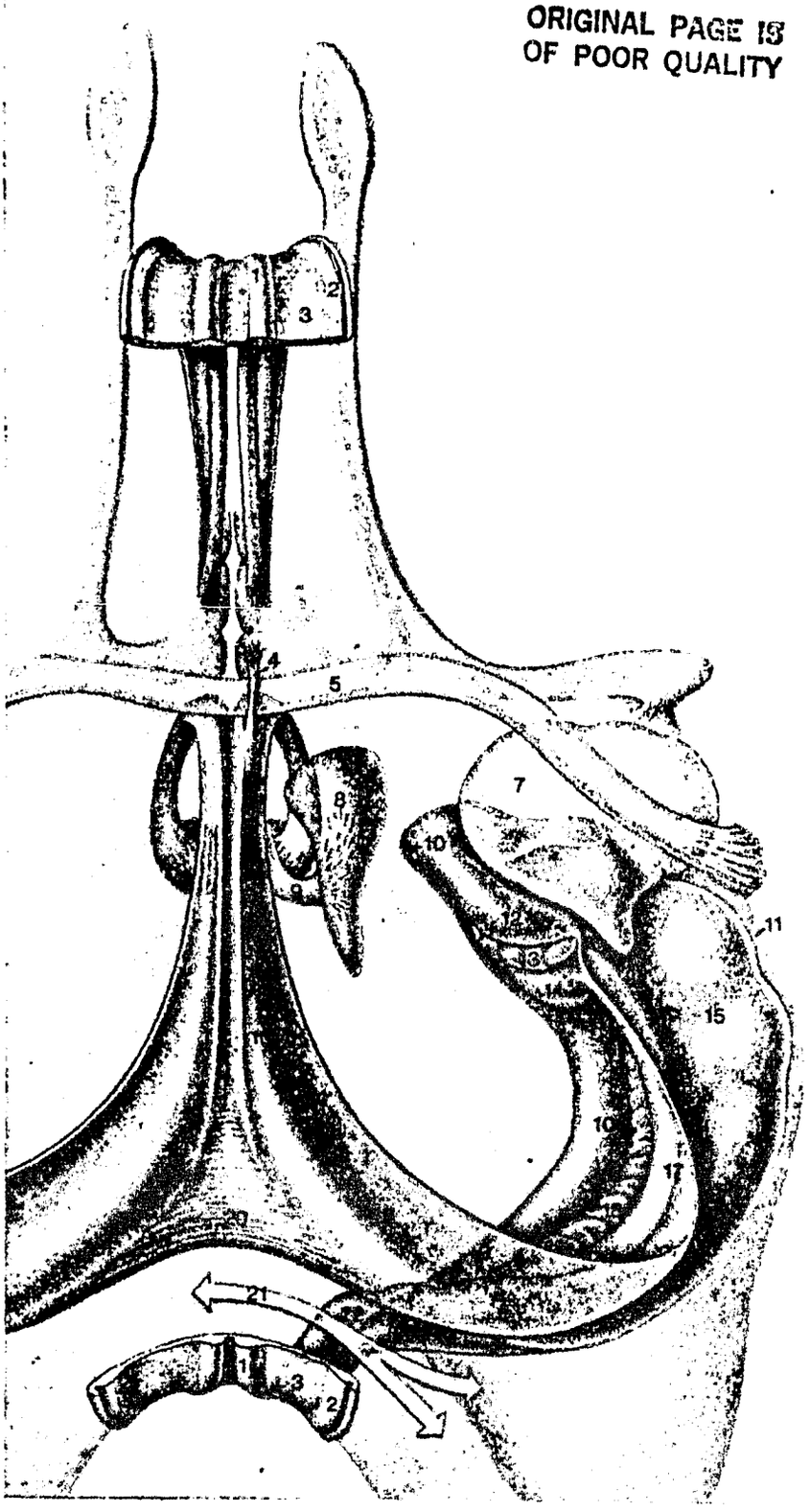
The fornix is a compact fiber bundle connecting the hippocampus with the hypothalamus and with various other structures (Figs. 12, 13). Its fibers first form the alveus, a thin white layer on the ventricular surface of the cornu ammonis, and then converge as the fimbria along the medial aspect of the hippocampus. Running posterosuperiorly, the fibers of the fimbria enter the crus of the fornix, a flattened structure that arches upwards and medially under the splenium of the corpus callosum. In this region a number of fibers decussate to the opposite side, thus constituting the commissure of the fornix



1 Stria longitudinalis medialis
2 Stria longitudinalis lateralis
3 Corpus callosum
4 Fornix
5 Taenia fornicis
6 Gyrus fasciolaris
7 Gyri Andreae Retzii
8 Hippocampus praecommissuralis
9 Gyrus dentatus
10 Alveus hippocampi
11 Fimbria hippocampi
12 Cornu ammonis
13 Digitationes hippocampi

14 Gyrus cinguli
15 Sulcus corporis callosi
16 Stria longitudinalis medialis } Hippocampus
17 Indusium griseum } supra-
18 Stria longitudinalis lateralis } commissuralis
19 Gyrus fasciolaris
20 Fasciola cinerea
21 Gyri Andreae Retzii
22 Cornu ammonis } Hippocampus
23 Subiculum } retrocommissuralis
24 Gyrus dentatus }
25 Sulcus hippocampi
26 Sulcus fimbriodentatus
27 Fimbria hippocampi
28 Gyrus intralimbicus
29 Limbus Giacomini
30 Sulcus hippocampi
31 Gyrus uncinatus

Fig. 12 Dissection showing the hippocampus and some related structures in oblique view from behind and above (2/1 ×)



1 Stria longitudinalis medialis
2 Stria longitudinalis lateralis
3 Indusium griseum
4 Fornix praecommissuralis
5 Commissura anterior
6 Columna fornicis
7 Corpus amygdaloideum
8 Nucleus anterior thalami
9 Tractus mamillothalamicus
10 Subiculum
11 Ventriculus lateralis, cornu inferius
12 Cornu ammonis (gyrus uncinatus)
13 Limbus Giacomini
14 Cornu ammonis (gyrus intralimbicus)
15 Cornu ammonis (digitationes hippocampi)
16 Corpus fornicis
17 Fimbria hippocampi
18 Gyrus dentatus
19 Crus formicis
20 Commissura fornicis
21 Site of corpus callosum
22 Gyrus fasciolaris

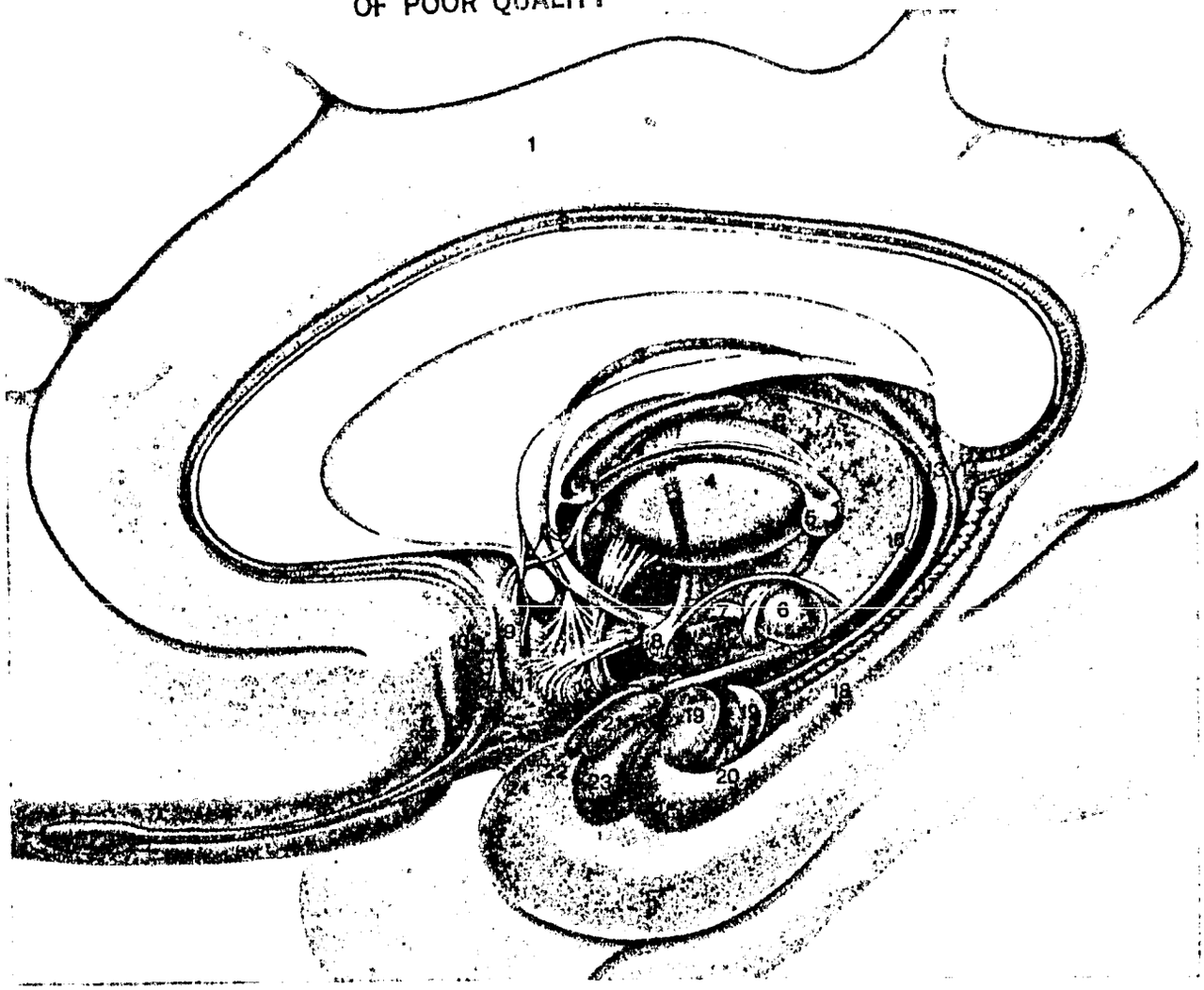
Fig. 13 The limbic structures isolated from most of their surroundings, seen from above (2/1 ×)

(Fig. 13). Proceeding rostrally over the thalamus, the two crura converge and join to form the corpus of the fornix, which lies immediately beneath the corpus callosum. However, at the level of the anterior pole of the thalamus the fornical corpus separates again into two bundles, the columns of the fornix, which curve ventrally in front of the interventricular foramen and caudal to the anterior commissure to enter the hypothalamus. Immediately behind the interventricular foramen a considerable number of fibers leave the column and pass backwards to the anterior nucleus of the thalamus and to the bed nucleus of the stria terminalis (Fig. 11). Other fibers split off from the fornix just above the anterior commissure and constitute a small precommissural portion of the fornix (Figs. 11 and 13). The main bundle of the fornix or postcommissural fornix finally transverses the hypothalamus, where most of its fibers terminate in the mammillary body (Figs. 4 and 14). The distribution of the fibers of these four groups is diagrammatically represented in Figure 11 and may be documented as follows:

(1) The precommissural fornix fibers originating from the cornu ammonis terminate exclusively in the lateral part of the septum.

(2) The precommissural fornix fibers originating from the subiculum are distributed to the lateral septum, the nucleus accumbens, the commissural hippocampus, and the frontal cortex.

(3) The postcommissural fornix exclusively contains, apart from some hippocampal afferents, fibers originating from the subiculum. Most of these fibers terminate in the mammillary body, anterior thalamic nucleus, and the ventromedial hypothalamic nucleus.



1 Gyrus cinguli
2 Indusium griseum
3 Stria terminalis
4 Nucleus medialis thalami
5 Nuclei habenulae
6 Nucleus ruber
7 Fasciculus telencephalicus medialis
8 Corpus mamillare
9 Septum verum
10 Area subcallosa
11 Gyrus diagonalis
12 Fibrae amygdalofugales ventrales
13 Crus fornicis
14 Gyrus fasciolaris
15 Fasciola cinerea
16 Fissura choroidea
17 Gyrus dentatus
18 Subiculum
19 Cornu ammonis
20 Site of limbus Giacomini
21 Nucleus corticalis amygdalae
22 Nucleus anterior amygdalae
23 Nuclei basalis + lateralis amygdalae
24 Cortex praepiriformis

Fig. 14 The structures of the limbic and olfactory systems and some input-output pathways as seen in a medial view (3/2×). Some displacement of structures serves to bring other structures in view. The walls of the third ventricle and the brain stem have been omitted almost completely; of the thalamus only the anterior, medial and habenular nuclei are illustrated

(4) The subiculum projects to various cortical areas, including the entorhinal area and parts of the adjacent medial temporal cortex, the retrosplenial and caudal cingulate areas and the caudal part of the medial frontal cortex. It is known that bilateral lesions of the hippocampus lead to a dramatic loss of recent memory. Lack of this disorder following bilateral fornix destruction may well be indicative of the relative importace of the direct subiculocortical efferents just mentioned. In addition to these cortical efferents the subiculum sends fibers to the amygdala.

The postcommisural fornix forms part of a closed system of centers and connections in which both the inner and the outer ring of the limbic lobe are involved. This system, which has already been discussed, is known as the circuit of Papez (Fig. 6). The structures constituting the outer ring, i.e., the cingulate and parahippocampal gyri, receive impulses from wide areas of the neocortex and convey these impulses by way of the cingulum towards the inner ring. Thus, it appears that the mesocortical outer ring positionally, structurally, and functionally represents a zone of transition between the neocortex and the allocortical, hippocampal inner ring.

B. Scopolamine and Amphetamine: Effects on Limbic Structures

Scopolamine increases ACh outflow in the cerebral cortex by an action on subcortical limbic structures. Cortical release of ACh by scopolamine is blocked by lesions in the septum, fornix, or fimbria of cats and rats (77,95,98) and by cortical undercutting (98). Lesions of the septal nuclei destroy the major cholinergic cell bodies that send afferents to the hippocampal limbic structures (Fig. 7). Lesions of the fornix (and fimbria) block

the non-cholinergic output of the hippocampus. It is believed that this non-cholinergic outflow eventually reaches the ascending cholinergic reticular system which projects to the cortex. It is reasonable to suggest that this interaction of the limbic system with the ascending reticular system is essential to the cat's ability to maintain arousal (92). Such a mechanism may involve in part, a pathway originating from the hippocampus that travels with the fibers of the fornix to the mammillary bodies in the hypothalamus. The major efferent connections of the mammillary bodies are via the mammillothalamic tract to the anterior thalamic nuclei. The nuclei of the anterior thalamus are non-specific nuclei that have extensive reciprocal connections with the association cortex (cingulate gyrus) (4,5,93,94). Lesions of septum, fornix, fimbria, and cortical undercutting may all impair the role that this thalamic radiation plays in maintaining arousal.

Amphetamine increases ACh outflow in the cerebral cortex by an action that also is dependent on an intact limbic system because septal lesions prevent the increase (98). Amphetamine induces short term increases in the level of ACh in the striatum and cerebellum and simultaneous decreases in the level of ACh in cortex and hippocampus (125). This is consistent with amphetamine-induced changes in the turnover of ACh. Although amphetamine can activate EEG by stimulation of the midbrain reticular formation, an intact reticular formation is not necessary for the drug effect. Ablation of the septum, which prevents amphetamine elicited release of ACh in the cortex, does not block the EEG activation. Apparently, at least two mechanisms exist for EEG activation by amphetamine.

Many collateral pathways are derived from the pathways linking hippocampal efferents with the anterior thalamus (Fig. 11). Fibers that leave the fornix and terminate in the anterior hypothalamic nuclei and the nucleus intercalatus in the mammillary bodies are of particular interest to the study of motion sickness. The anterior hypothalamic nuclei exert a major influence on the visceral organs. The predominantly parasympathetic outflow from this region will increase sweating, vasodilation, salivation, and peristalsis of the gastrointestinal tract while decreasing heart rate and blood pressure. All of these peripheral effects can and do occur in motion sickness. The nucleus intercalatus sends efferent fibers to the area postrema which in turn innervates the vomiting center (112,141). The apparent blockade of the septohippocampal pathway by scopolamine could both diminish the peripheral symptoms of motion sickness and block neuronal pathways to the vomiting center.

C. Neurochemistry

1. Cellular Neurochemistry

Cholinergic input from cell bodies located in the septal area is distributed to basal or apical dendrites near the somata of pyramidal and granular cells. Electrophysiological evidence has confirmed that this input is excitatory. Hippocampal neurons also are excited by glutamate via other excitatory pathways such as the perforant pathway from the entorhinal cortex (Fig. 7) and the hippocampal commissural fibers. Inhibitory axosomatic terminals are present on these neurons and probably are derived from the basket cells which most likely employ GABA as their inhibitory neurotrans-

mitter (126). Lesions of the hippocampus will reduce the concentrations of glutamate by 25% in the septum along with significant decreases in entorhinal cortex, nucleus accumben septi, mammillary bodies and in the contralateral hippocampus as well. These investigations support a role for glutamate as a transmitter in the limbic system (99).

The hippocampus contains bursting-type (pyramidal) cells which display atropine-sensitive muscarinic excitation and both bursting and non-bursting (interneuronal) cells which display d-tubocurarine-sensitive nicotinic inhibition (128). Hippocampal muscarinic receptors appear before the development of any cholinergic input from the septum. Amygdala kindling results in a decrease in the level of hippocampal cholinergic muscarinic receptors which occurs with and without septal lesions that destroy cholinergic input to the hippocampus. Septal lesions, however, do not cause loss of muscarinic binding capacity. Considering these findings, it has been suggested that muscarinic receptors are down-regulated by depolarization of the hippocampal neurons (26) and not dependent upon the integrity of cholinergic innervation.

Nicotinic cholinergic receptors have been identified in rat hippocampus in the polymorphic cell layer of the fascia dentata and the stratum oriens. They have not been identified in the outer molecular layer of granular cells of the fascia dentata, in the pyramidal cells of Ammons, the fimbria or fornices (106) (Figs. 7 and 12). Other investigators have concluded that hippocampal pyramidal cells are responsive to muscarinic and some nicotinic agents and that these agents are not acting at two independent receptors (12).

2. Neurochemical Mechanisms

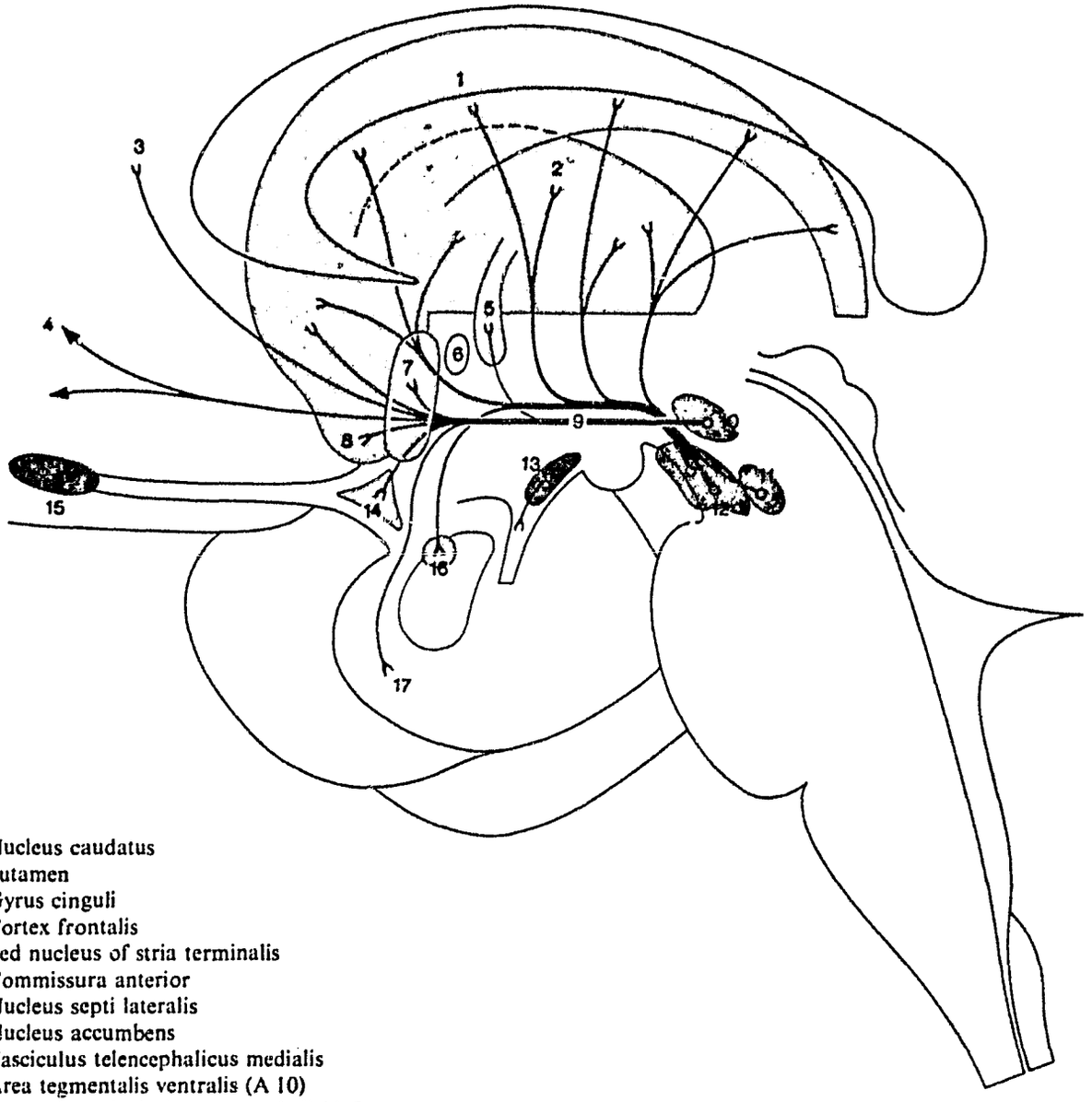
Stimulation of hippocampal muscarinic receptors with the cholinergic agonist oxotremorine causes a rise in the content of ACh in the hippocampus and a decrease in its rate of synthesis, implying decreased release of ACh. Because this action is blocked by drugs that interfere with noradrenergic transmission, the apparent oxotremorine-induced increase in the turnover-rate of NE in the region has been implicated as a mediator of the drugs' effect on release of ACh in the hippocampus (74). Presumably, stimulation of cholinergic receptors in the hippocampus results in the inhibition of the release of septal ACh or a decreased responsiveness in hippocampal cells to ACh through an intermediary release of NE. Further support for this scheme comes from the work of Segal and Bloom (129) who reported that the activity of hippocampal neurons was inhibited by loud auditory stimuli (stress) or electrical stimulation of the locus coeruleus, which is the origin of a well established inhibitory noradrenergic input pathway (Fig. 8) to the hippocampus (62). The stimulatory effects of amphetamine as an anti-motion sickness drug on noradrenergic transmission in the hippocampus is similar to the effects of scopolamine in that both drugs ultimately block excitation of hippocampal neurons. The fact that each drug possesses nearly equal anti-motion sickness properties, has entirely different neurochemical effects, and yet, exerts synergistic effects when combined, supports the hypothesis that the limbic system is a critical center in the CNS for initation of motion sickness.

Amphetamine not only facilitates noradrenergic transmission, but also is a potent releaser of dopamine (DA). It turns out that DA also exerts a tonic inhibitory tone on the cell bodies of septo-hippocampal cholinergic neurons

(Fig. 15). Release of DA in the septum is probably the mediator of prolactin's effects in decreasing the turnover rate of ACh in the hippocampus, striatum, and thalamus. DA is believed to be the prolactin inhibitory factor so its release in the medium eminence by prolactin would constitute a negative feedback loop. Clearly, both NE and DA, as released by amphetamine, exert inhibitory influences on hippocampal cells.

Stimulation of the (mesencephalic) reticular formation (Fig. 10) increases ACh release from the hippocampus. Section of both fornices does not alter spontaneous release of ACh from the hippocampus, but does prevent release mediated by the reticular formation. The administration of amphetamine acts exactly like stimulation of the reticular formation; the increased release of ACh is also prevented by section of the fornices. Scopolamine also increases ACh release from the hippocampus. This release occurs following topical applications of the drug and occurs with or without cut fornices. It appears that the pharmacological action of scopolamine is not dissimilar from section of the fornices.

Wood and Cheney (146) have attempted to distinguish whether a neuronal feedback loop or a presynaptic muscarinic receptor mechanism could be invoked to explain the actions of scopolamine on the turnover rate of ACh in the septo-hippocampal cholinergic pathway. They concluded that the cholinergic systems of the hippocampus and thalamus possess self-regulating feedback mechanisms (Fig. 6) that are markedly perturbed by muscarinic receptor blockers. The perturbation is expressed by a two-fold elevation in the turnover of ACh in the hippocampus. They described experimentation in support of this conclusion that: (1) ruled out the presence of presynaptic muscarinic



1 Nucleus caudatus
2 Putamen
3 Gyrus cinguli
4 Cortex frontalis
5 Bed nucleus of stria terminalis
6 Commissura anterior
7 Nucleus septi lateralis
8 Nucleus accumbens
9 Fasciculus telencephalicus medialis
10 Area tegmentalis ventralis (A 10)
11 Formatio reticularis mesencephali (A 8)
12 Substantia nigra, pars compacta (A 9)
13 Nucleus infundibularis (A 12)
14 Tuberculum olfactorium
15 Bulbus olfactorius (A 15)
16 Nucleus centralis amygdalae
17 Cortex entorhinalis

Fig. 15 The dopaminergic system

binding sites in the hippocampus, (2) negated any role of inhibitory cholinergic neurons in the septum, and (3) demonstrated that the blockage of the stimulatory noradrenergic input to the septum (Fig. 8) does not influence the increased turnover rate of ACh in the hippocampus that follows scopolamine administration. The authors suggested that axonal collaterals of the cholinergic septal neurons may activate noncholinergic inhibitory interneurons which in turn act on the cell bodies.

3. Regional Metabolism

The deoxyglucose technique has been employed to determine which brain regions become metabolically active after stimulation of limbic structures. The technique uses elaborate radiotracing methodologies to identify changes in the cellular uptake of glucose which are used as a measure of metabolic activity. Stimulation of the ventral subiculum demonstrated increased activity in the amygdala, hypothalamus, and basal forebrain. Specific hypothalamic regions included the ventromedial, dorsal, posterior, lateral, premammillary, and preoptic nuclei. Earlier work using older axonal transport methodology has revealed the presence of direct projections to the ventromedial region and mammillary nuclei (Fig. 11). Presumably the additional hypothalamic regions are activated by secondary projections from these centers. Stimulation of the ventral or dorsal hippocampus demonstrated increased activity in the lateral septal nuclei by the deoxyglucose technique (69). Projections from the hippocampal gyrus have been reported as excitatory (111).

One of the consequences of hippocampal cell discharge, as induced by cholinergic stimulation, is the large rise in the levels of cortisol in blood that occurs regardless of the phase of the animal's circadian rhythm. Application of other neurotransmitters such as 5-hydroxytryptamine (5-HT) or NE into the dorsal hippocampus does not lead to a change in the concentration of glucocorticoids in the blood. Blockers of choline uptake, such as hemicholinium-3, will inhibit the noise (stress) induced rise in circulating glucocorticoids, presumably via interference with necessary cholinergic mechanisms (2).

The value of drugs that inhibit the uptake of synaptosomal choline by presynaptic cholinergic terminals, particularly those terminals located in the hippocampus, has been indicated by the experimental finding that stimulation of the septum for one hour (60 Hz) did not lead to a change in the concentration of hippocampal ACh, but if 100 µg of hemicholinium-3 was first given intraventricularly, a 50% reduction in ACh resulted within 7.5 minutes. Recovery to normal levels occurred three days later (129).

D. Limbic Systems (Layman's Summary)

The limbic system embodies a number of specialized brain regions which, through extensive interconnections, give meaning to such concepts as memory, learning, attention, emotion, stress, and autonomic behavior. Centers of volition and consciousness (frontal cortex) directly influence the processes of memory and learning (hippocampus) which in turn exert control over centers mediating stress (pituitary), autonomic functions (hypothalamus and brain stem) and attention (reticular formation). While these relationships are

complex there are, nevertheless, sufficient clues to identify those regions that may be particularly critical to the etiology of motion sickness. For example, transmission between the septum and hippocampus is especially sensitive to anti-motion sickness drugs like scopolamine and amphetamine, and to the physiological actions of such hormones as ACTH and cortical. Modulation of the flow of nervous impulses to the hypothalamus and midbrain reticular formation (area postrema and chemotrigger zone) may underscore changes that occur in an individual's motion sickness susceptibility or in his expression of motion sickness symptoms after the administration of these drugs. The limbic system may be described as a nervous system through which the significance of environmental stresses are translated into hormonal, adaptive, and autonomic responses.

IV. STRESS

The general adaptation syndrome has been introduced and defined (73) as an integrated complex of adaptive reactions to cope with changing or stressful external conditions. It's not merely a transitory emergency adjustment to changes in environment, but an adaptive reaction which comprises the learning of defense against future exposure to stress, and helps to maintain a state of adaptation once this is acquired. The hypothalamic-pituitary-adrenal axis is central to the physiology of stress. The main metabolic effects of glucocorticoids have been known for years. They involve tissue and enzyme-specific changes, mediated by induction of new protein synthesis at the gene level, which elevates blood glucose, free amino acids, and free fatty acid levels via breakdown of principally muscle and fat tissue. This apparently supplies the organism with the necessary energy and building blocks to affect whatever adaptive or repair responses are required. We are interested in understanding the roles of the hypothalamic-pituitary-adrenal axis in adaptive learning and behavior. Thus, we will focus on the actions of these hormones on the brain. There is no reason to assume that changes in the constitution of normal blood components, as mentioned above, do not play definitive roles in brain metabolism. Consideration of these factors, however, is outside the scope of this report.

It has been stated that the primary mediator underlying the pituitary-adrenal cortical response to a variety of stimuli may simply be the psychological apparatus involved in emotional or arousal reactions to threatening or unpleasant factors in the life situation as a whole (13). There is no doubt that a reciprocal connection exists between septo-

hippocampal and pituitary-adrenal systems. The response of the pituitary-adrenal axis to changing external environments is definitely modified by the hippocampus, but the actual role of the hippocampus in controlling ACTH release seems to be determined by a variety of known and unknown modalities of the external environment, and the milieu interieurre of the hippocampus itself. The adaptive role of the hormones seems to be to enhance remembering, if the contingency of the situation requires retention or repeated retrieval, and then to enhance forgetting, unlearning, or extinction of the experience in order to make a place for acquisition of new adaptive responses when environmental changes make them necessary. The large number of observations on hippocampal function suggest that the system must be intact in order to adjust behavior to new requirements under circumstances of environmental uncertainty. In other words, the hippocampal formation, by suppressing older memories allows new actions to be taken, new memories to be formed. The hormones seem to modulate the motivational properties of conditioned external and internal modalities. Thus, increasing the motivational value of conditioned stimuli results in doing the response again, while decreasing this value results in not doing the previous pattern in order to make a place for acquisition of new experience (13).

V. HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

A. Introduction

It is important to understand the relationship between the limbic system and the hypothalamic-pituitary-adrenal axis. This chapter will discuss how limbic system stimulation or lesions change the responses of the hypothalamic-pituitary-adrenal axis to stress and novel environments (e.g., zero-gravity). It will indicate the specific locations within the limbic system that bind the stress hormones (ACTH, cortisol), how these hormones modulate limbic system activity, and in particular, the modulatory effect this has on the hypothalamus. The behavioral effects of these hormones, lesions, and various environmental stresses also will be considered. Taken together, the data further define the role of the limbic system as a center of adaptation, learning, and sensory integration. More completely, these data establish the merit of manipulating and understanding the pituitary-adrenal cortical system in the prevention of motion sickness.

B. Physiological Role in Stress

The hypothalamic-pituitary-adrenal axis can be stimulated by stress, direct electrical excitation of the hypothalamus, or by humoral agents such as epinephrine (EPI) or histamine (HISM). The influence of the limbic system on the hypothalamus generally has been regarded as inhibitory because stimulation of the hippocampus, the dorsal hippocampus, hippocampal fields CA1 and CA2, or the dentate fascia results in a diminution of the hypothalamic-pituitary-adrenal axis response to stress, to stimulation of the hypothalamus, or to

application of these humoral agents (13,60). Stimulation of the hippocampus, however, does not affect the basal secretory levels of the pituitary-adrenal hormones. This observation may distinguish the limbic system as a mediator of the impact that psychological stress has on the hypothalamic-pituitary-adrenal axis as contrasted with basal, circadian or blood-borne mechanisms.

Glucocorticoids exert potent modulatory influences on the activity of the limbic system. Particularly high levels of cortisol bind in the hippocampus, especially in the ventral hippocampus and hippocampal CA1 and CA2 subfields (60,83). Some glucocorticoid binding occurs in the amygdala, lateral septum, induseum griseum, anterior thalamus (parafasciculari nucleus) and neocortex (83). The hormone reduces the output of the dorsal hippocampus and attenuates the rise in ACTH release that ordinarily follows stimulation of the reticular formation. The theta wave is also diminished by cortisol (83). Pyramidal cell output declines along with electrical activity in both the dentate fascia and dorsal hippocampus (13,60). Cortisol implants into the reticular formation, amygdala and medial thalamic nuclei curtail the rise in ACTH that follows stressful environmental change but implants into the ventral hippocampus reportedly augment this response (60,83). It appears that stimuli enhancing secretion of ACTH are modulated by the levels of glucocorticoid in the limbic system and possibly other brain regions as well. The system apparently does not function strictly in a negative feedback capacity in that adrenal cortical hormones released by ACTH modulate limbic mechanisms that influence ACTH release by complex and as yet poorly understood means.

Ablation studies have tended to support the notion that most limbic structures exert inhibitory influences on the responses of the hypothalamic-

pituitary-adrenal axis to different stressful environments or stimuli. Hippocampectomy intensifies an experimental animal's reaction to stress and exaggerates this animal's adrenal response (96). The afternoon rise of ACTH in the rat following hippocampal lesions has been interpreted as support for an inhibitory role for the limbic system (145). Other researchers have likened dorsal hippocampectomy with lesion of the fornix (the principal output of the hippocampus) in that both lesions impair the ability of dexamethazone to attenuate stress-induced and basal responses of the adrenal glands (46). Interestingly, ventral hippocampal lesions were without effect. A number of investigators have shown that fornicotomy blocks the normal rise in cortisol that occurs during extinction or in response to a novel environment (zero-gravity?). Furthermore, this lesion blocks the action of ACTH, which ordinarily inhibits extinction of a conditioned avoidance response (102). Lesions of the medial septum destroys the theta rhythm after 30 days, whereas, a month after lesions of the lateral septum a conspicuous rise in glucocorticoid receptors in the hippocampus can be noted along with an inability of the animal to acquire conditioned avoidance responses (100).

It is difficult to reconcile these data and make any specific and definite assertions concerning the functional interconnections between the limbic system and the hypothalamus. It is likewise difficult to understand the specific modulatory roles of cortisol and ACTH in the central nervous system on the basis of these data alone. There are a few observations that may serve to guide us in understanding the functional role of the limbic system. Specifically, the projection of the limbic system onto the hypothalamic centers often inhibits the stress response and this influence is modified by cortisol and ACTH.

C. Neurochemical Theory

Our knowledge of the actions of specific pharmacologic agents on neurotransmission in the limbic system and hypothalamus is useful in determining how our more effective anti-motion sickness drugs work at a neurochemical level. Cholinergic involvement along the hypothalamic-pituitary-adrenal axis is well documented. Nicotine elevates circulating levels of both ACTH and cortisol (23,27) whereas carbachol, when applied to the dorsal hippocampus, raises the concentrations of cortisol in the blood. Carbachol can counteract the effects of dexamethazone which otherwise reduces the level of cortisol (2). The effects of stressful noise on enhancing the release of cortisol can be inhibited by drugs that interfere with cholinergic transmisson through blockade of choline uptake (e.g., hemicholinium-3) (2). Cholinergic mediated release of corticotropin releasing factor (CRF), although it can be partially blocked by muscarinic blocking agents like atropine, is inhibited in a dose dependent manner by nicotinic antagonists (27). Because ACTH and cortisol affect many aspects of neurotransmitter metabolism, it is important to understand these effects and to correlate these effects to the neurochemical actions of such proven anti-motion sickness drugs as scopolamine and amphetamine.

The cholinergic tract that connects cholinergic cell bodies in the medial septal nuclei with pyramidal cell bodies in the hippocampus is one of the best studied cholinergic tracts in the CNS and is referred to as the septohippocampal pathway. Scopolamine blocks muscarinic cholinergic receptors located on the pyramidal cells causing a compensatory increase in the release of ACh by the septohippocampal tract in a futile attempt to overcome that

blockade. The exact mechanism of this compensatory rise in the turnover rate of ACh in the hippocampus is not completely understood (146). Stimulation of inhibitory noradrenergic or dopaminergic input to the septal nuclei by feedback neurons somewhere downstream from the hippocampus may be blocked by scopolamine. The muscarinic agonist, oxotremorine, ordinarily enhances the activity of these feedback neurons (74). Amphetamine-induced release of dopamine (DA) and norepinephrine (NE), according to this scheme, should and actually does attentuate septohippocampal transmission, although it does so by a different neurochemical mechanism than scopolamine.

These observations represent our best understanding to date of anti-motion sickness drug mechanisms at a neurochemical and neurophysiological level and allow us to explain why such pharmacologically diverse drugs as scopolamine and amphetamine are both effective by themselves and synergistic when administered simultaneously. This point can not be overemphasized, it has and will be reiterated throughout this report, for it embodies the essence of neurochemical theory as it is used to understand brain function. Essentially, once a particular neurochemical event has been identified and correlated with the phenomenom of motion sickness in any capacity, then it follows logically that the determination of other means to effect the underlying neurochemical events will naturally hold promise, representing new approaches to the same end of modulating motion sickness susceptibility. Specifically, we know that scopolamine blocks transmission in the septohippocampal pathway. This particular neurochemical event has been identified and negatively correlated with the phenomenon of motion sickness. Because scopolamine exerts a pharmacological action at many other locations, it is necessary to correlate activity in the septo-hippocampal pathway by additional means with other

phenomena of motion sickness. This has been done. Amphetamine releases DA and NE which in turn inhibits transmission in the septo-hippocampal pathway. Furthermore, blockade of this pathway by scopolamine or amphetamine impairs the ability of the limbic system to influence key hypothalamic centers involved in the expression of the symptomatology of motion sickness and the hormonal responses to stressful motion. What has been done here is to correlate certain pertinent physiological and hormonal counterparts of motion sickness with transmission through the septo-hippocampal pathway. This directly links specific aspects of the pharmacology and physiology of motion sickness in terms of this central pathway.

The side effects that follow the administration of scopolamine include loss of short-term memory, amnesia, an inability to concentrate, focus attention and learn, and modification of normal behavioral reactions to novelty (119,139). Anticholinergic drugs apparently attenuate habituation to novelty (51,54) and reduce preferences for, and reactions to novelty (63). Stated differently, novelty does not motivate the scopolamine-treated animal or individual, in effect, the novel environment is not really well learned or remembered, and is not given too much attention. Stimulation of the septo-hippocampal pathway, therefore, might be critical to man's reaction to the microgravity of space and, just like the sleeping individual, when man is somewhat detached from his sensory world he is less likely to react strongly to it, to be motivated by it, or become motion sick in response to it. The psychology of motion sickness is linked to the neurophysiological and adaptive responses of motion sickness and to the septohippocampal pathway by this reasoning. This connection is more abstract than those previously made, but this is to be expected when one stops talking in terms of molecular and

cellular events and instead addresses particular qualities of mind and conscious experience.

D. Stress Hormones, Neural Mismatch and Adaptation

Now that most of the available data has been directly tied to septo-hippocampal transmission within the limbic system and now that we have intimated a possible intrinsic psychological mechanism in the expression of motion sickness susceptibility, it is appropriate to introduce the concept of the limbic system as a neural mismatch center or sensory-comparator center. The hypothesis, stated most simply, states that the limbic system is a center in which incoming sensory information is compared with stored, past experience and from which the appropriate behavioral and physiological responses to that comparison are elicited. Depending upon the polarity of the comparison, the appropriate response may range from unmotivating familarity to stressful novelty. When the disparity is great, the individual will have to learn to adapt to the new environment, hence, mechanisms of memory and associative learning will be initiated. It is the intention of the authors in the remainder of this chapter to investigate the precise mechanisms of actions of ACTH and cortisol in these mechanisms of memory and associative learning, in the regulation of septo-hippocampal transmission and in effecting the neuro-chemical changes within specific neuronal systems.

Following exposure to a stressful environment, the usual sequence of release of stress hormones proceeds according to a specific pattern. First, corticotropin releasing factor (CRF) is released from the hypothalamus, presumably by stimulation of certain cell bodies in the region. The hormone

is released from axonal terminals located on or near the median eminence, a highly vascularized portal system communicating with the anterior pituitary gland. Second, CRF stimulates release of ACTH from the anterior pituitary. The whole molecule of ACTH ($ACTH_{1-39}$) can then be carried via the systemic circulation to the adrenal glands where the release and production of glucocorticoids is enhanced. The principal glucocorticoid in man is cortisol; in the rat it is corticosteroid. Finally, cortisol exerts a wide range of actions on most tissues of the body, mainly through an interaction with the genetic apparatus of the individual target cells. Generally, this action results in changes in the biosynthesis of particular cellular proteins or enzymes; an effect realized over a period of days. This outlines the classical sequence of events.

The classical understanding of the hypothalamic-pituitary-adrenal axis is oversimplified. It does not account for the fact that ACTH and other peptide hormones reach and have actions on the brain itself (43,50,55,88,123) or that certain peptide fragments such as $ACTH_{1-10}$, $ACTH_{4-10}$, and $ACTH_{4-7}$ exert actions on the central nervous system and yet are devoid of peripheral (adrenal) activities (15,42,121). Specifically, ACTH administered intraventricularly or directly onto the hippocampus will enhance the turnover rate of ACh. This action is not expressed following direct application to the septal nuclei (147). A decrement in the turnover rate of ACh in the hippocampus actually has been reported following intraseptal application of ACTH (19).

ACTH or adrenalectomy (which elevates ACTH) is known to increase the turnover rate of NE, whereas, removal of the pituitary gland causes a decrease

in the turnover rate (142). Behaviorally, ACTH improves acquisition of conditioned avoidance responses and diminishes extinction (13). $ACTH_{4-10}$ and $ACTH_{1-24}$ accelerate the turnover rate of DA (9,42) and increase the specific activity of tyrosine nydroxylase and dopamine-beta-hydroxylase (in hypothalamus). Cortical dopamine-beta-hydroxylase declines (42). The effects of cortisol on the septo-hippocampal pathway have been described as generally inhibitory.

Cortisol is known to exert an influence on the metabolism of a number of different neurotransmitters in the CNS. Cortisol will significantly reduce the biosynthesis of choline acetyltransferase, the enzyme responsible for synthesizing ACh. This action is opposed by insulin which by itself heightens enzyme-specific activity. Levels of tyrosine hydroxylase, the enzyme responsible for the synthesis of DA and necessary for the eventual biosynthesis of NE and epinephrine (EPI) as well, are expanded by cortisol at the same time (127). The absolute levels of dopamine-beta-hydroxylase, the enzyme which converts DA into NE in noradrenergic neurons, also are increased by this glucocorticoid and decline after adrenalectomy (60). Furthermore, phenethylamine-N-methyltransferase (PNMT), which converts NE into EPI in the adrenal medulla and in epinephrinergic neurons also is augmented by the presence of cortisol (60,83).

Summarizing these data, the effects of cortisol on the metabolism of DA, NE, and ACh are consistent with the actions of the anti-motion sickness drugs, amphetamine and scopolamine, in that both enhance DA and NE impair cholinergic transmission. The difference is that cortisol acts over a period of days as an adaptive influence whereas the anti-motion sickness drugs are acutely

active in less than one hour. It should be noted that the drug action is not natural, indeed, there is evidence that scopolamine elicits a compensatory rise in the turnover of ACh (146) and in the number of postsynaptic receptors in an attempt to overcome the blockade (68,108,131). In addition, amphetamine induces a compensatory decline in the levels of tyrosine hydroxylase (70).

Other transmitter systems are impacted by cortisol as well. The levels of tryptophan 5-hydroxylase are elevated and an increased ability to convert tryptophan into 5-hydroxytryptamine (5-HT, serotonin) has been measured (13). Removal of the pituitary gland will cause turnover of 5-HT to decline (42). Because tryptophan 5-hydroxylase, the enzyme limiting the rate of 5-HT synthesis, is not saturated in vivo with its substrate, tryptophan, variations in the levels of blood tryptophan, or more specifically, variations in the ratio of blood tryptophan to other amino acids competing for uptake into brain, directly influence 5-HT synthesis (90,138,150). There has been one report that NE, but not EPI can inhibit induction by cortisol of hepatic tryptophan pyrollase (132). Other work (53) has shown that hydrocortisone decreases brain tryptophan and 5-HT concentrations. This is due to increased activity of the hepatic enzyme tryptophan pyrollase, which metabolizes tryptophan and causes a decrease in the concentrations of free and total plasma tryptophan, which in turn, results in decreased concentrations of tryptophan in brain.

Lesion of the raphe nuclei influences the circadian fluctuations in circulating levels of ACTH. The cell bodies of central 5-HT secreting neurons are all located in the raphe nuclei within the brain stem reticular system (Fig. 9). The lesion smooths out the rhythm, reducing the amplitude of the

peaks and troughs, without shifting or eliminating the rhythm. The projection from the raphe nuclei to the suprachiasmatic nucleus of the hypothalamus or mediated by the limbic system and the fornix might be responsible for this effect (18,137,142). Interestingly, it has been observed that vacillations in the levels of ACTH correlate inversely with those of 5-HT for up to three days after adrenalectomy (140) and fluctuations in the levels of cortisol and 5-HT follow a similar rhythm in hippocampus, amygdala and frontal cortex (13). Weiner and Ganong have reviewed the data and raised the possibility that serotonergic neurons affect circadian fluctuations in ACTH secretion via the limbic system or suprachiasmatic nuclei (142). However, 5-HT administered directly into the dorsal hippocampus does not modulate the levels of cortisol (2). Furthermore, 5-HT does not alter release of CRF.

The influence that ACTH and cortisol have on neurons secreting gamma-aminobutyric acid (GABA), is particularly important because GABA is a ubiquitous inhibitory neurotransmitter present throughout the brain. Cortisol increases the level in cortex of glutamic acid decarboxylase (GAD), an enzyme which directly biosynthesizes GABA, and increases GABA-transaminase, the enzyme which catabolizes GABA (60,83). An inhibitory gabaergic input to the medial septum has been described that when activated attentuates release of ACh in the hippocampus (60,115). The pyramidal cells in the hippocampus also are innervated by inhibitory basket cells which employ GABA as their neurotransmitter (83). It is possible that cortisol, by affecting these cells as well, would also diminish the excitatory influence of the cholinergic septo-hippocampal pathway on the pyramidal cells in the hippocampus. Adrenalectomy elevates the number of GABA-uptake receptors in the brain while cortisol reverses this effect (86). The reduced level of receptors present on

synaptic terminals means that cortisol prolongs the time which GABA would have to exert its inhibitory influence on post-synaptic neurons. This action of cortisol is consistent with its effect on GAD and GABA-transaminase in that inhibitory gabaergic transmission is facilitated. Drugs which increase the release of GABA in the septum only, such as delta-9-tetrahydrocannabinol, the active ingredient in marihuana, have been shown to specifically reduce the turnover rate of ACh in the hippocampus (115). It is reasonable to assert that cortisol acts in part through gabaergic neurons to inhibit impulse flow through the septohippocampal pathway. The effects of cortisol again appear to oppose those of $ACTH_{4-10}$ because $ACTH_{4-10}$ is known to reduce the absolute concentrations of GABA throughout the hindbrain, midbrain, and cortex (42). Reduced levels of GABA would imply impairment of the wide-spread inhibitory function of this neurotransmitter.

Summarizing this section on stress hormones, neural mismatch and adaptation, it has been demonstrated that the stress hormones ACTH and cortisol exert adaptive influences on the limbic system through both fast acting receptor-mediated mechanisms and via slow acting plastic changes in neurotransmitter metabolism. The modulation of neurotransmission by cortisol was likened to the action of the anti-motion sickness drugs scopolamine and amphetamine and found to differ in time of action only. The limbic system model of neural mismatch was further defined and substantiated through elucidation of the adaptive effects of the stress hormones and by recognition of the relationship between the hypothalamus and the septohippocampal pathway.

E. Hypothalamic - Pituitary - Adrenal Axis (Layman's Summary)

The hippocampus exerts an inhibitory action on the hypothalamus which modulates the influence of stress, adrenaline, and histamine on the hypothalamic-pituitary-adrenal axis. These stressors generally lead to increased release of the stress hormones ACTH and cortisol. Scopolamine and amphetamine, acting individually or synergistically through different neurochemical mechanisms, can impair cholinergic input to the hippocampus from the septum which in turn diminishes the hormonal responses of the hypothalamus to stress. Thus, both the behavioral and hormonal components of stress are reduced, respectively. Neurochemically, the actions of scopolamine and amphetamine appear to be mimicked by cortisol but antagonized by ACTH. The similarity between the neurochemical actions of cortisol, scopolamine, and amphetamine is revealed by the complementary influences these agents have on the synthesis, degradation, and activity within several neurotransmitter systems. Experimental manipulation of the levels of corticol, ACTH or ACTH-like peptides may therefore modulate motion sickness susceptibility in man.

VI. NEURAL MISMATCH THEORY

The involvement of the hippocampus in working memory has been distinguished from reference memory (101). Short-term memory has been defined as a working memory roughly analogous to consciousness. The information held in short-term memory may be rehearsed, which will keep it in short-term memory or move it into long-term memory. Consolidation processes are integrative processes which are believed to organize and categorize new information with previously stored information. A two stage discrimination learning theory has been proposed which includes: (1) attention, a perceptual process mediated by sensory analyzers, and (2) response attachments, based on reinforcement (9). Clearly, events with effects mediated by the hippocampus relate to the development and/or violation of expectancies about motivationally significant stimuli (67).

The hypothesis that the sensory conflict or neural mismatch theory of motion sickness has a neurophysiologically defined meaning within the context of the limbic system, as described above, seems tenable. The limbic system might be imagined as a sensory-comparator, poised at the interface of ongoing sensory experience and long-term, stored experience. It functions by comparing present experience with past and when entrainment of new memory is intended, this new memory is organized and categorized by association with past memories. An example of this process would be the memorization of a four-digit telephone extension number wherein the new number is associated with an identical number already in long-term storage but which originally represented the street address of a friend. This kind of associative process is intuitively obvious and practiced by all of us. The essential principle

here is that new information is learned by identification of its pattern and by the subsequent association of this pattern with established patterns in long-term storage. Certainly, this conceptualization of the memory process, as well as any other, must be regarded as a working hypothesis at best because of the lack of definitive evidence in support of these contentions. These conceptualizations can serve useful purposes, however, in that they provide frameworks into which additional information can be fit and evaluated for consistency with the original conceptualizations. This, in effect, is the scientific method, a deductive process by which a given hypothesis is continually refined to accommodate the available data. Long-term memory might even be aptly considered a hypothesis or conceptualization about the nature of reality, on an individual basis, and which operates and expands by a similar deductive process. The subsequent paragraphs will present a model of processes underlying an individual's reaction to zero-gravity and will interpret the available information within that conceptual framework.

The model of sensory conflict or neural mismatch which results in motion sickness might be defined by neurophysiological responses of the limbic system. Specifically, the limbic system takes immediate sensory information, compares it with past experience and initiates necessary adaptative responses on the basis of that comparison. The sensitivity of the system to this function is of course influenced by such factors as arousal or attention; factors which in themselves are part of the adaptive responses initiated. The environment of zero-gravity results in a novel sensory experience which, when compared to past experience, stands in conflict with reality. An adaptive response is initiated which, because of the strength and extent of the sensory novelty, is accompanied by the vomiting response. Money (56) has forcefully

argued that this response is a normal response to being poisoned. The assumption is that gross mismatching of sensory experience underlies this response and that the mechanism has been preserved in the genome as a survival-related mechanism of evolutionary benefit because the sensory distortions that often follow the ingestion of poisonous substances cause emesis, and hence, evacuation of the poisonous substance from the system. While this interpretation is intuitively pleasing on a conceptual level, it is not amenable to direct experimental testing. However, the hypothesis that a reduced inhibitory input to hypothalamic centers, as mediated by the limbic system, may comprise a major part of the neurophysiological mechanisms leading to the symptoms of motion sickness, can be directly tested.

It has already been indicated (above) that the proven anti-motion sickness drugs act by reducing the activity of the cholinergic septohippocampal pathway by two independent neurochemical mechanisms. Because scopolamine also inhibits the establishment of long-term memory from short-term or ongoing sensory experience, it follows that the adaptive responses to novelty might also be attenuated. This has been experimentally determined through measurement of the responsiveness of the hypothamic-pituitary-adrenal axis to stress. Specifically, scopolamine inhibits the rise in cortisol that ordinarily follows psychological and physical stress (27). Scopolamine therefore appears to be overriding normal adaptive responses of cortisol to stress and may neurochemically function in a fashion similar to cortisol.

Because muscarinic cholinergic septohippocampal transmission is directly blocked by scopolamine, the identification of a neurochemical action of cortisol that exerts a similar effect would be additional evidence in support

of the hypothesis that the limbic system embodies a major portion of the neurophysiological mechanisms responsible for the symptoms of motion sickness. An action of cortisol on the limbic system has been experimentally and neurochemically defined and involves plasticity changes in inhibitory gabaergic neurons impinging upon septal cholinergic cell bodies. Adrenalectomy causes a rise in the quantity of presynaptic GABA uptake receptors, an effect that is reversed by the administration of cortisol (86). The ability of cortisol to reduce the specific-activity of choline acetyltransferase, the enzyme which synthesizes ACh in all cholinergic neurons, further indicates that the neuropharmacological effects of scopolamine can be functionally replicated by cortisol. The ability of cortisol to increase the specific-activity of tyrosine hydroxylase, dopamine-beta-hydroxylase and phenethylamine-N-methyltransferase, the enzymes responsible for the biosynthesis of DA, NE and EPI, respectively, also draws attention to the possibility that the neuropharmacological effects of amphetamine may be functionally mimicked by cortisol as well.

VII. CONCLUSIONS AND SUMMARY

This report has described the functions of the limbic system in terms of performance, memory, learning, extinction, discrimination, reactions to novelty, and sensory experience. The limbic system has been characterized as a neural mismatch center in which present sensory experience is compared to long-term memory stores and evaluated for internal consistency. Essentially, environmental cues are recognized as novel or familiar and the complex behavioral reactions of adaptation or extinction are initiated in accordance with the motivational or attentional state of the animal. Neural mismatch is not defined in this report as it has been in previous research on motion sickness. Previous research has referred to such concepts as "a mismatch between vestibular and visual inputs", or "a mismatch between otolith and semicircular canal organ input" or simply to " the mismatch neuron". While this concept of sensory-conflict is very popular among researchers in the field, it has not been properly or realistically evaluated or defined.

This report has presented evidence that the limbic system model of sensory conflict or neural mismatch theory is a good working hypothesis that may be of potential value in the development of new approaches to the study of motion sickness. Manipulation of the hormones of the pituitary-adrenal cortical system is just one example of a new approach to the study of motion sickness that holds promise. Experimentation with these hormones is recommended on the basis of our understanding of the neurochemical actions of these hormones and the similarity of these actions with the neuropharmacological effects of such anti-motion sickness drugs as scopolamine and amphetamine.

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