DRUG ACTION ON THE BRAIN-STEM RETICULAR FORMATION[1]

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INTRODUCTION

Since the pioneer work of Magoun and his associates in the early forties, the reticular formation of the medulla, pons, and mesencephalon has been recognized increasingly as a major integrative and regulatory system of the brain. In particular, the research centered about the role of the reticular formation (RF) in the maintenance of sleep-wakefulness cycles has provided unified concepts embracing the disciplines of anatomy, physiology, psychology and communications

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biophysics. Pharmacologists have therefore turned their attention to the reticular core of the brain stem to seek the possible site and mechanism of action of the pharmacological agents which have powerful influences on consciousness, on emotionality, and on delicately balanced sensory and motor integration. It is the purpose of this paper to review the large volume of accumulated experimental data on drug action on reticular mechanisms. A review of such data, however, seems to require first a clear definition of the brain mechanisms under consideration and then a brief discussion of the general reliability of present avenues of neuropharmacological investigation in this area. This paper will thus attempt a synthesis of present views of the anatomical arrangement and physiological function of the reticular formation (RF). Other areas (non-specific thalamic nuclei, related gray matter of the diencephalon, hypothalamus, septum and rhinencephalon) have been often considered to form a part of the ascending reticular activating *system* (ARAS); the "centrencephalon" of Penfield and "mesodiencephalic system" of Himwich are examples. The reviewer considers the RF as anatomically defined below to exhibit pharmacological sensitivities different from those of the other regions mentioned. Physiological and pharmacological evidence reviewed in this paper will therefore be confined to that in the RF itself. Space considerations have prevented citation of many physiological and neuropharmacological papers when these have been adequately reviewed in major symposia. No attempt has been made to consider the clinical data from which specific drug activity in the brain stem is deduced. Also, important papers may have been missed because of the widely divergent publications in which neuropharmacological studies appear. For these omissions the reviewer wishes to apologize at the outset.

The anatomical term, "reticular formation," refers to the heterogeneous mass of cell bodies enmeshed in a network of dendrites and axons located in the central core of the medulla, pons, and mesencephalon. It includes all the gray matter not belonging to cranial nerve nuclei, cerebellar relay nuclei, and lemniscal relay nuclei. It is an extension of the spinal gray matter, to which it is ontogenetically related, and anteriorly disappears into subcortical nuclei, particularly those of the diffuse thalamic projection system.

The physiological role of the RF is in keeping with its general interneuronal organization. Neural aggregates of this important integrating structure contribute to the control of respiration, vasomotor tone, gastrointestinal function, temperature regulation, and neuroendocrine mechanisms. More generalized regulatory functions are exerted in the sleep-wakefulness cycle, in reception, conduction and integration of sensory inflows, and in extra-pyramidal motor outflow systems.

As the view of the central nervous system (CNS) as a huge telephone switchboard has gradually been abandoned, newer concepts have emerged of an infinitely variable, multi-faceted organization in which integrative functions are not assignable to a radio-control room in the cortex. Symposia and reviews on this subject have accumulated rapidly. Many aspects of the RF function were examined in detail in 1957 in the symposium "Reticular Formation of the Brain"

(200) and in the earlier "Brain Mechanisms and Consciousness" (81). More recently, important reviews of specific functional aspects have appeared in the "Handbook of Physiology," Volumes I to III (106), and in the abstracts from the 20th International Congress. Major reviews from Europe (11, 329) and South America (346), as well as from this country (111, 112, 262, 263, 264, 265, 266, 267, 300), including Magoun's recent monograph "The Waking Brain" (268), emphasize the international distribution of work in this field. With regard to neuropharmacological investigations, the most complete review of the action of drugs in the CNS since 1949 (375) is that of Wikler (399). French (110), Segundo (346), Himwich (174, 175, 179), and Bradley (44) have contributed reviews of drug effects specifically on reticular mechanisms. The author refers the reader to these monographs for complete bibliographies and to Baker (18) for most recent articles.

I. FUNDAMENTAL CONSIDERATIONS OF STRUCTURE AND FUNCTION

A. Anatomical investigations of structure

Almost from the beginnings of microscopical descriptions of the brain the term "reticular formation" has been applied to the ill-defined core of the brain stem surrounded by long fiber tracts and nuclei of sensory systems. A careful histological study led Ramón y Cajal (67) to conclude that reticular cells were not all functionally similar but comprised both third-order sensory neurons and second-order motor neurons. The neurons vary from 10 to 90 micra in length of soma; the axons and dendrites are very variable in length. The most extensive studies of cyto-architecture of the RF in recent years are those of Olszewski and his group (279, 301, 302), who have centered their efforts on the identification of individual cell groups, using Nissl staining techniques. A very large number of individual nuclei were identified in the human RF, but a physiological significance has yet to be assigned to these cell aggregations. Brodal (59, 60, 61, 62) and his co-workers have concentrated on identification of lateral tegmental and paramedial reticular nuclei. Most of the identified cell aggregations have been diagrammed by Rossi and Zanchetti (329), who concluded that a major mediolateral subdivision may be made in the medullary and pontine RF; however, in the midbrain the division is less clear. The medial portion is characterized by large and even giant neurons, whereas the lateral division contains smaller cells throughout.

Caudal projections. By use of modified silver stains of degenerating fibers following localized lesions, Brodal (61), Nauta and Kuypers (299), and others (*cf.* 329) have shown reticulo-spinal connections to arise from all types of reticular cells, those from the giant cells of the pons being most numerous. Ipsilateral connections arise exclusively from the pons, while both ipsilateral and contralateral projections arise from the medial two-thirds of the medullary region below the nucleus of the seventh nerve and above the inferior olive (377).

Rostral projections. Reticular neurons projecting to the hypothalamus and to septal nuclei of the limbic system are located in the caudal midbrain and ascend in two separate bundles. Other major efferent tracts travel to the cerebellum and,

in fact, are best considered a specialized part of the reticular system (329). The longest ascending efferent paths have been traced in the tract of Forel and appear to arise to a large extent in the medulla and pons (299). They occupy a central position posteriorly, shift laterally as they enter the midbrain. Eventually ascending bundles are displaced dorsally to the red nucleus and may correspond to the central tegmental tract in primates (299). Anatomical evidence suggests that reticular ascending pathways divide and project toward the cortex, some turning ventrally into the subthalamic nucleus and others turning dorsally to interlaminar nuclei (303, 332, 336, 337).

Nauta and Kuypers (299) concluded that there are abundant short fibers which terminate at each level and constitute the multi-neuronal, short-axon system of reticulo-reticular connections which is so often considered to be the basis of selective drug sensitivity in the RF. The beautiful Golgi preparations from young animals by the Scheibels (337), however, tend to oppose this general concept. They have painstakingly illustrated the arrangement of dendrites and axons of individual reticular cells and their interconnecting relationship with other reticular cells and with incoming afferents. They could find no evidence of short-axoned, Golgi-type II cells, but instead were able to show that most, if not all, reticular axons project far up or down the brain stem. Indeed, axons were often bifurcated with both rostral and caudal projections, thus extending the sphere of influence of certain individual cells from spinal cord to diencephalon. Other reticular cells showed extensive dendritic arborization (336) to make a multiplicity of synaptic contacts with afferents from the spinal lemniscus, spinoreticular tracts, uncinate bundle of Russell, interstitial motor cells of the bulb, corpora quadrigemina, pyramids, trapezoid bodies, and the like. The Scheibels (337) stressed that afferents enter in a plane perpendicular to the long axis of the brain stem and parallel with the dendrite arbors of reticular neurons. Both axons and dendrites show richly branching patterns of collaterals so that the number of cells with which any one reticular cell may synapse becomes astronomical. The RF is thus considered to be a polysynaptic path for transfer of information in terms of a manifold lateral dispersion. But the Scheibels could not concur with views that multiple short-axon cell links transmit the bulk of reticular influence caudad or rostrad. They suggested that slowly transmitted impulses may travel in axons of very fine caliber or by circuitous paths through reticular collaterals.

Brodal (61) pointed out that, despite the complexities of its neuronal networks, the RF is not altogether diffusely organized. Nuclei projecting exclusively to the cerebellum (nucleus reticularis tegmenti, n. reticularis lateralis, and n. reticularis paramedianus) should be considered as separate from the remainder of the RF, which shows some mediolateral differentiation (61, 63). Only medial portions of the RF contain cells with long efferent connections to regions outside the RF itself. Furthermore, most descending paths originate in regions of pons and medulla rostral to those having ascending connections. Ascending fibers to the hypothalamus arise in large number from the midbrain, and those to the basal ganglia from its anterior portion, while thalamic and subthalamic connections arise chiefly in the bulbar RF (299).

On the basis of present anatomical knowledge, however, one must conclude

that cells of the RF having similar connections are not always organized into stereotaxically localizable regions or precise nuclei; instead, descending and ascending projections may be intermixed; similarly afferent inputs may be widely dispersed along the axis of the RF, intermingling with collaterals from other sources. These features of reticular organization add much difficulty, both in tracing pathways by electrical or chemical stimulation techniques and in interpreting pharmacological effects.

B. Afferent connections

Despite anatomical descriptions of afferent collaterals into the RF as early as those of Kohnstamn (329), Ramón y Cajal (67), and Allen (8), the important role of this region as an extralemniscal sensory system was not recognized clearly until direct excitation of reticular neurones by collaterals from each sensory modality was demonstrated (116, 118, 367, 368). Auditory, visual, olfactory, and various somatic sensory as well as widespread visceral inputs, including vagal and vestibular, have been identified. Specific experimental data on each modality have been extensively reviewed with full bibliography [Rossi and Zanchetti (329), pages 322 to 324]. The pathways were shown generally to have long conduction times (1.5 to 3 meters per second), although not invariably (116). Potentials recorded from reticular areas were high-amplitude, slow waves rather than the sharply peaked potentials typical of lemniscal pathways (116). They appeared to have long recovery times relative to those recorded in major sensory paths (232).

Not only do collateral fibers carry responses from all modalities of sensation, but most other areas of the brain are represented; afferents from the hippocampus (4, 5, 6) and septum (298) and from cerebellar areas (112) are numerous. Neocorticofugal inputs were recognized somewhat later as an important contribution to the integrative functions of the RF. The collateral inputs from corticospinal and corticobulbar tracts described anatomically by Ramón y Cajal were identified physiologically by several groups. Pathways originating from sensorimotor, frontal, and occipital oculomotor fields, cingulate gyrus, orbital surface, superior temporal gyrus, and temporal tip were carefully mapped by electrical and chemical stimulation of discrete cortical areas in curarized monkeys (113). In the cat prepared with cord transection at the first cervical segment (*encephale isolé*), Bremer and Terzuolo (58) mapped similar reticular inputs from somatosensory, paravisual, auditory, and suprasylvian areas. Frontal, sensorimotor, and cingulate projections to the brain stem (328), sensorimotor connections (166), and entorhinal inputs were also described at about the same time (5, 6). Earlier descriptions of corticofugal connections based on anesthetized preparations are difficult to interpret in view of pharmacological evidence of reticular sensitivity to anesthetics. They have been reviewed in detail by French (109).

From the studies of input paths, the convergence of stimuli on reticular neurons became apparent. Both summations of electrical responses from neuronal populations, recorded from macroelectrodes, and single unit firing can be recorded in the RF. Modifications of reticular potentials can be demonstrated following stimuli applied to many points in the central nervous system. There is evidence

of facilitatory (58) or inhibitory interaction (116) between incoming stimuli from differing sources. Any single unit may be facilitated, inhibited, or remain the same when stimulated through different sensory modalities (338) or from the cerebellum (238). The microelectrode studies have been elegantly reviewed by Moruzzi (294) and by French (112). An interesting feature of recent studies has been the recognition that some *but not all* input paths converge on each particular neuron (166). It has appeared conceivable that the *constellation* of reticular cells responding or not responding may serve to identify the input (338). On the other hand, reticular neurons responding to many inputs may function in generalized reticular activities while those neurons whose temporal discharge patterns differ according to input may serve for localization or identification or both (9, 10).

C. Special neural aggregations for autonomic integration

Although as stated earlier the nuclear masses outlined in the RF by some investigators have not been correlated with specific functions as yet, certain areas of the RF have become identified with specific autonomic functions. A detailed analysis of these functions and the physiological and pharmacological investigations thereof encompasses the entire brain stem and is therefore too large a subject for inclusion here. A brief outline, however, will be included since localized electrical stimulation in the RF often activates these functions as well as the integrative mechanisms on which drug action may be under test in any particular pharmacological study.

Throughout major portions of the RF, for example, electrical stimulation will elicit marked influences on blood pressure, respiration, and even on heart rate. Bach (16) early described the vasomotor inhibitory and facilitatory regions as medial-posterior and lateral-anterior, respectively. However, in later works (17) he was unable to substantiate the view that inhibition of reflex activity and lowering of blood pressure and respiratory rate, or *vice versa*, are necessarily linked. Thus vasomotor and respiratory regulatory activity in the RF has not yet been identified in precise centers. Somewhat similar lack of correspondence was reported by Domino (90) who reviewed much early work.

A comparison of areas giving vasomotor responses (278, 387), respiratory responses (308), and reflex alternation of postural tonus (270), as described by Rossi and Zanchetti (329) is useful as a starting point, but technical variations are so important that direct comparisons are not really valid. Much of the literature on these localizations has been summarized relatively recently (106, 329).

The beautiful work of Wang and Borison (38, 382, 383, 384, 385) has outlined within the RF a chemoreceptor trigger zone for emesis and a center for the integration of vomiting reflexes. Many drug studies have been directed to an analysis of the compounds eliciting emesis by action on one or both of these sites.

D. Efferent connections—functional role of the reticular formation in central nervous system regulation

Anatomical description of efferent connections has been given new perspective by physiological studies of various sensory and motor phenomena. This review

will concern itself with three major generalized influences of the RF. The first of these is the ascending reticular influence on the state of awareness of the organism, on sleep-wakefulness cycles, and on consciousness. Second is the widespread reticular influence on the propagation of sensory stimuli from receptor to receiving area of the primary systems. The third aspect of reticular function is its role in the extrapyramidal motor system. The important integrative function of the RF in autonomic and neuroendocrine regulation will not be considered in detail since this involves for the most part localized reflex functions and activities of circumscribed areas, and because adequate discussion involves review of work on the entire brain stem and on rhinencephalic connections as well. Obviously, the influence of the RF on behavior is inextricably a part of its influence on each of these other functions. Its role in learning *per se*, however, will be considered separately (K.F. Killam, in preparation). No definite data on drugs are yet available for review.

1. Regulation of the sleep-wakefulness continuum. Bremer (55) should be credited with the recognition that the waking state is dependent on influences ascending through the brain from below the level of the superior colliculi. That low-voltage, fast activity in the EEG and behavioral awakening could be elicited by sensory stimulation was reported earlier (95, 318), but it was not until 1949 that Moruzzi and Magoun (295) clearly delineated the central role of the RF in arousal mechanisms. Direct stimulation of the RF with frequencies of 60 to 300 per second induces low-voltage, fast activity in the EEG (295) and behavioral awakening (247) similar to that obtained by olfactory, auditory, visual, tactile, and visceral afferent stimuli (329). In awake animals an alert attitude is elicited with similar stimulation, while high-voltage stimulation appears to be "unpleasant, even frightening" (347). Lesions in the direct sensory paths were shown not to alter wakefulness, while both acute (246) and chronic (115, 247) reticular lesions in the midbrain precipitated coma-like conditions. Thus, areas in which lesions prevent normal wakefulness seem to be congruent with those in which afferent stimuli evoke long latency potentials and which upon direct stimulation induce wakefulness (115). Later it was shown that neocortical stimulation was able to reproduce the electroencephalographic and behavioral effects of afferent or reticular stimulation (58, 348). Arousal responses, however, could be elicited only from those areas from which single responses in the RF could be evoked. Unit analysis indicates that on afferent stimulation the frequency of firing of reticular cells is increased and new cells are recruited into activity during the arousal process (253). Cerebellar stimulation has a similar effect (282).

Although the major importance of these and many other contributions from the same laboratories remains unassailed, the past five years have brought a sharper delineation of the problem of the maintenance of wakefulness. Sharpless and Jasper (350) have suggested that the brain-stem RF functions primarily in the maintenance of long-lasting arousal patterns; they have termed this function "tonic" in contrast to the rapidly shifting "phasic" alerting mechanisms located in the diencephalon. However, the comatose condition typical of animals with chronic reticular lesions is not permanent under certain conditions (1, 139, 364). Such data vary from clinical experience (108) and contradict findings in shorter

term experiments. Since lesions were serially placed, the capacity of the mammalian brain for retraining or rerouting of normal pathways may be involved.

The most striking finding in this field since the original, and now classic, contribution of 1949 (295) is a recent description of a dual mechanism in the reticular formation. Studies involving the mapping of very carefully localized lesions indicated that perhaps the trigeminal inflow was primarily responsible for the maintenance of tonic reticular activity (326). The criteria used were sleep-wakefulness patterns in the EEG of the *encephale isolé*. Later work from the same laboratories (20, 21, 22) reported that lesions just ahead of the trigeminal, but slightly caudal to those of Roger *et al.* (326), induced a waking rather than somnolent EEG. Thus, the fifth nerve input is by no means essential even in the absence of spinal inflows. Cordeau and Mancia (72) later showed that hemisection of the brain stem at any level between this pretrigeminal area and the n. paraolivaris medialis produced asymmetrical cortical EEG patterns. On the side of the section there was persistent desynchronization in contrast to synchrony on the contralateral side. Removal of visual and olfactory inputs failed to abolish wakefulness (23, 260). Further work (20) eliminated the possibility that increased CO_2 levels or blood pressure effects were involved. The existence of an area in the RF inducing high-voltage, slow-wave EEG patterns was confirmed by Magnes *et al.* (259), who demonstrated that low-frequency stimulation of the medullary RF slightly anterior to the nucleus paraolivaris medialis in the region of the nucleus of the tractus solitarius produces EEG synchronization. Thus, it appears possible that there are intrareticular mechanisms for fine control that regulate subtly both degrees of awareness and levels of sleep. Further evidence for this relationship has been provided by Bonvallet and Bloch (30, 32, 33). Using both localized lesions and local procainization they demonstrated phasic ascending inhibitory influences derived from areas in the medullary RF triggered by and influencing the activity of the pontine and mesencephalic RF. Jouvet and Mounier's studies (203, 207, 208, 209) of cats with pontine and bulbar reticular lesions also emphasize the importance of the interplay between different areas of the RF in the regulation of electrical activity at various levels of sleep.

Opposing the general view of an active arousal process originating in the RF is Hess' concept of a "sleep centre." Spindling and slow waves in the EEG and behavioral sleep were reported to be induced by appropriate stimulation of areas of the hypothalamus and midbrain (7, 171, 285). The best explanation of these opposing findings appears to the reviewer to be that while thalamocortical circuits are most certainly capable of synchronized rhythmic firing and probably represent the recurrent paths for spindle bursts, they operate autonomously unless interrupted by ascending reticular influences. These "arousing" influences can, under special conditions, be counterbalanced by driving the thalamocortical circuits at their optimal frequency. It is beyond the province of this review to attempt a more detailed analysis of the problems of sleep and the origin of the electrical activity associated therewith. Numerous special reviews on these topics are included among the reviews already listed.

2. Modulation of incoming signals. Although anatomical findings had raised

previously the question of the possibility of central influence on sensory receptors (67), Granit and Kaada (147) first provided physiological evidence of such regulation in their study of muscle spindles. Muscle spindle discharge was enhanced by stimulation of lateral and anterior parts of the RF but inhibited by stimulation of medial bulbar areas. The lowest threshold for motor facilitation appeared to occur at the gamma efferent loop. These studies have been extended by Eldred *et al.* (99, 100), and control of motor outflow has been reviewed (98).

Early evidence of alterations in sensory potentials within the central nervous system at the first synaptic relay was obtained by Hagbarth and Kerr (153) who demonstrated an inhibitory effect of the RF on afferent potentials elicited by dorsal root stimulation. Similar data were reported by Linblom and Ottosson (245), and evidence of reticular influence at various other sensory relays appeared rapidly. Sensory signals were shown to be blocked at the nucleus gracilis (170) and in the sensory nucleus of the fifth nerve (168). Optical responses were demonstrably reduced at the lateral geniculate nucleus (57, 170), even though retinal firing was enhanced (146). Following RF stimulation, auditory responses to clicks were depressed at the geniculate (57) and at the cochlear nucleus (128, 206). Indirect evidence of a similar mechanism in the olfactory system has been reported (214). Decreases in facilitatory interaction at thalamic synapses were also described (232).

Questions have been raised regarding the interpretation that the collected data show the RF to exert an inhibitory action on the transmission of sensory information in major paths (329). When the receptor was bypassed and nuclei within the sensory paths were stimulated directly, Bremer and Stoupel (56) reported facilitation of sensory responses by reticular stimulation. They considered depressant effects of the RF to be due to occlusion or to be indirect, *via* cortical arousal. Dumont and Dell (94) also found facilitatory effects on *centrally elicited* sensory responses, and enhancement of cortical firing in response to light has been reported to follow mild RF stimulation (127). Some recent studies by Hugelin *et al.* have suggested that reticular inhibitory influences on auditory pathways are due to contraction of muscles of the inner ear (191, 192). However, Galambos and his group (296) have opposing data; furthermore, many of the studies by Magoun's group were done on completely curarized preparations.

Naquet reported (297) that RF effects on the iris itself may explain reduction of optic potentials recorded in the geniculate nucleus following RF stimulation. Since RF inhibitory effects on cortical recordings of the same potentials remained after atropinization of the eye, the significance of these data in terms of physiological mechanisms is not yet clear.

The catholic nature of the inhibitory influence at the first synapse of the sensory path for all modalities, the repetition of such results after total curarization, the temporal sequence and long-lasting duration of depression in some experiments, and the evidence (from pharmacological blockade or destruction of the RF) of a tonically maintained inhibition (153, 168) all suggest a true inhibitory process. Experience of the author coincides with that of Jouvet and Desmedt (206), however, which indicates that the area of the RF inhibiting sensory re-

sponses is much more limited than that generating ascending impulses which induce EEG and behavioral arousal. Extensive reviews by Hernández-Peón (163), Granit (145), and Livingston (249) discuss these data in detail.

The experimental findings indicating a reticular inhibitory influence on afferent signals derive functional significance when alterations in the responses to repetitive stimulation are analyzed. In terms of conscious sensory perception, repetitive signals tend to be handled in two specific ways. These may be, as Hernández-Peón has pointed out (163), selective "attention" to meaningful stimuli or "afferent blockade" of the non-meaningful. There is evidence of a reduction of potentials in a particular modality during "attention" induced by signals of a different modality (169), or by reticular stimulation (170). Hernández-Peón and his co-workers and the Galambos group explored these phenomena in unanesthetized, freely moving animals bearing implanted electrodes. The term *habituation* has, unfortunately, from the pharmacologists' point of view, been applied to the phenomenon of gradually decreasing response at central sensory synapses to an unvarying repetitive signal. Gradual decrease and then disappearance of responses at the cochlear nucleus to click stimuli (129, 167, 169), of geniculate responses to photic stimuli (164, 165), and even of EEG arousal responses to tone (350) have been demonstrated. The "habituation" or "familiarization," as the reviewer prefers to term the phenomenon, disappears when "consequence" is added to the signal or when a novel stimulus is introduced. It also disappears during states of depressed reticular function [for example, during sedation with pentobarbital and following lesions of the RF (167)]. Some opposite findings have, however, been reported by Huttenlocher (193), who found no change in cochlear responses in sleep and wakefulness. Exact recording sites may be critical since anatomical connections differ in dorsal and ventral cochlear nuclei. Furthermore, Sokolov (360) suggested that "habituation" phenomena may require dual pathways, of which one is a stable referent.

3. Modification of motor outflows. Current interest in the brain-stem reticular formation may be said to owe its origin to Magoun's observation in 1944 (261) that stimulation of the bulbar reticular formation inhibited on-going motor activity. The weight of early evidence suggested that two-neuron stretch reflexes, polyneuronal flexor reflexes, and cortically induced motor movement were universally inhibited by descending influences from the medial portions of the bulbar RF (248, 269, 277), and by stimulation of inflow pathways to this area, such as the cortex (277), caudate nucleus (248), and cerebellum (180, 357, 358, 359). Spasticity, tremor, and other exaggerated reflex activity such as that following decerebration could also be affected. In contrast, stimulation of more anterior parts of the medial RF through the mesencephalon, and of the lateral bulbar and mesencephalic RF, caused facilitation of motor activity (261). Again early work emphasized a catholic action on all types of motor activity (248, 270, 319).

Later work has brought out the importance of reciprocal mechanisms; while some points of stimulation either inhibit or facilitate motor activity generally, many more have been shown to produce reciprocal effects. Opposing reticular effects on the patellar and jaw-opening (linguomandibular) reflexes (231) were

suggested as evidence of a differentiation between influences on flexor and extensor reflexes. Gernandt and Thulin (140) came to similar conclusions regarding reciprocal effects on antagonistic muscles and joints. Sprague and Chambers (362, 363) showed such reciprocal effects to be important in maintaining posture. Hugelin (185) confirmed the findings that jaw reflexes were inhibited by the so-called facilitatory area of the brain stem, but considered the site of inhibition to be the afferent limb of the reflex (185) or at the interneuronal pool (190), and thus related to RF effects on sensory input already described. He also found the general area affecting motor activity to be directly superimposable on that causing ascending activating effects, and thus considered that all three functional output systems are inseparably related in the RF (186). Other studies on reciprocal effects suggested that an ultra-short period of inhibition precedes long-lasting facilitation of the monosynaptic reflexes during inhibition of polysynaptic reflexes (237). In further analyses of this phenomenon, Hugelin and Bonvallet (187, 188, 189) studied the jaw-opening and -closing reflexes by recording motor nerve action potentials in unanesthetized cats. They found that facilitatory effects of RF stimulation are rapidly controlled by antagonistic inhibitory effects. These controls are abolished by anesthetics including chloralose, under which most previous work had been done. Freezing or removal of the major part of the cortex had similar effects, which led to the view that inhibitory influences have a diffuse cortical source and may be related to ascending activation of the EEG. However, as Magoun (268) has pointed out: "thus far inhibitory effects have not been reproduced in intact waking animals, indicating that important facets of extra-pyramidal motor control remain to be delineated."

Certain hyper-reflexic conditions are now considered to result from disorders in reticular activity. Removal of inhibitory influences by isolation of the bulbar RF from its more anterior inflows (388) or by destruction of descending paths involving spinal interneuronal relays (270) results in unopposed or even enhanced facilitatory downflows. These may be the mechanisms involved in rigidity and spasticity (268, 270) except in the case of decorticate spasticity, which could be explained by the Hugelin-Bonvallet hypothesis of a diffuse cortical inhibitory control. Postural tremor appears to be associated with increased reticular activity. It has been suggested to result from abnormal timing of reticulo-spinal impulses with consequent synchrony of motor firing (263), or from a "denervation sensitization" of cholinergic mechanisms (112, 201, 389). The abnormal interaction of rhinencephalic and ascending influences in the RF has recently been discussed as a source of tremor (2). The major importance of the extra-pyramidal motor system and the central role played by the RF has been reviewed by Jung and Hassler (210), who pointed out that "one tends to forget during the present vogue of brain mythology about consciousness and attention that the reticular formation is mainly a motor coordinating center, the lower part for respiration, the higher parts for eye movements and body posture. The psychological effects of attention and conscious acts are only secondary specializations derived from basic reticular functions controlling motor behavior and preponderant solely from an introspective and anthropocentric viewpoint."

II. METHODOLOGICAL CONSIDERATIONS IN DRUG RESEARCH

The investigations of the selective sensitivity of the RF to pharmacological agents have employed two criteria. First, neurophysiological approaches have been used to detect alterations in the electrical activity of the RF *per se* or of structures or pathways functionally related to the RF. Secondly, behavioral studies have been concerned with drug-induced alterations of unpatterned or conditional behavior. Secondarily and by inference, drug effects on the RF have been hypothesized. Attempts to make both types of measurement simultaneously provide perhaps the most meaningful data. The obviously important biochemical approach which should be added to the above methodologies has not been productive as yet. Some of the difficulty stems from the problem of physically separating a sample of RF tissue which may be analyzed for enzymological differences and drug sensitivities in comparison to other brain areas. Perhaps more importantly, there is little evidence available for any biochemical substratum of activity of drugs on specific brain areas. Further, the accumulation *per se* of a drug in any area does not necessarily indicate activity at that site.

In neurophysiological investigations, drug influence can be assessed from alterations in potentials evoked within the RF by stimulation of various inflow pathways, or alterations in generalized or local responses to reticular stimulation may be measured elsewhere in the brain. Obviously, while drug effects may be more meaningful if attached to functional circuits of these kinds, localization of effect must be inferred from studies of patterns evoked simultaneously in different pathways. Use of potentials evoked within the RF by stimuli directed to portions of the RF itself adds a certain degree of confidence of local action, but loses functional significance. Moreover, any influences on inputs to the region might alter reticulo-reticular conduction indirectly. Thus investigators often *infer* that drugs act directly on the RF, from data which are more properly considered evidence of pharmacological alteration of its integrative functions. It is often not clear whether drugs altering reticular outflows are affecting cells of origin within the RF itself, efferent paths, reception of the efferent signal, or its functional expression.

Many general features important to drug research with neurophysiological methods have been reviewed (220, 376, 399). The importance of experimental control of influences of body temperature, blood pressure and local blood flow, oxygenation, *etc.*, have been emphasized. Similarly, complexities in interpretation of data when anesthetics, atropine, or antihypotensive agents are given have been amply discussed. The possibilities of central effects of paralyzing agents must be evaluated. While these restrictions may seem obvious, it is remarkable how many of the papers reviewed herein ignored one or more of these problems.

There are still more elusive complications which arise with interpretation of neurophysiological and behavioral data obtained even under the most ideal experimental conditions. The use of recorded electrical activity as a criterion of function in various parts of the brain immediately raises the question of single cell *versus* population recordings—that is, the relative merits of micro- *versus*

macro-electrodes (277). It is certainly true that drug action on fundamental components of brain activity (brief all-or-none spikes, graded slow waves, and potential gradients) must be examined. The basic kinetic operations as defined by Fessard (105): "conduction of impulses along fibers, transmission of excitation or inhibition across synapses, electrotonic spread and ephaptic interactions and finally rhythmic generation of potentials" must eventually be subjected to scrutiny in the presence and absence of drugs. Such data contribute to knowledge of fundamental modes of action of drugs on neurons in general. Nonetheless, with the present state of our knowledge regarding transfer of information in the brain, the selective action of drugs on a functional part of the brain such as the RF can hardly be established by the study of drug action on single cells in isolation. As Brazier (54) has stated, we are faced with two models of information coding. Whether we accept the deterministic model, which assumes a massive computational analysis of individual unit responses or the probabilistic model, for which "the profile of activity in a population of neurons . . . is the determining factor," techniques for *simultaneous* recordings from hundreds of single units will be required to estimate drug effects on structures of such diversity of activity as the RF. Until many individual units can be simultaneously sampled, evaluation of drug effects on functioning units of the brain can be done only in analog fashion by measuring the influences of drugs on the summation response of many neurons, that is, with macroelectrode recording techniques.

A number of laboratories have attempted to pinpoint drug action by the use of simultaneous macro-recordings in various pathways, by using a series of different preparations in the same species and under the same conditions, or by the use of animals with various lesions. Dell (83) has drawn attention to points of technique in neuropharmacological research and has listed a series of lesions which can be used to delineate drug action: 1) prebulbar section, separating bulbar inhibitory reticular formation from anterior structures; 2) premedullary section, leaving the brain-stem facilitatory mechanisms connected to the cord; 3) transpontine section, leaving important parts of the reticular system connected to the cortex; 4) prepontine sections, the classical *cerveau isolé*, with continuously spindling EEG; and 5) diencephalic sections, destroying all reticular connections to the thalamus and cortex. To these may be added spinal animals with cord transected at the first cervical vertebrum (*encephale isolé*). Bradley, Elkes, and their co-workers have compared drug studies in the intact, conscious cat with implanted electrodes with those in intact, curarized cats and monkeys and with *encephale isolé* and *cerveau isolé* preparations (44, 47, 49, 50, 51). They have added some unit studies to their recordings of brain-wave patterns with macroelectrodes. Himwich and his group (177, 179, 324) have compared intact rabbits with rabbits in which the hemispheres are separated from the brain stem, in order to localize drug action in what they have termed the mesodiencephalic system (RF plus diffuse thalamic projection nuclei). Monnier and his co-workers (131, 283) have developed a series of preparations in rabbits using the Hess implanting technique and have compared thresholds with evoked single and multiple potentials, amplitudes of response, and duration of afterdischarge. Their sites of

stimulation have included the RF and thalamus as well as rhinencephalic structures. In our laboratories, successive stimulation of a series of sites in the brain stem and recording of responses at brain-stem and cortical levels have been utilized in individual experiments, with a view toward separating the sites of drug action. Beginning efforts have been made to measure drug effects simultaneously on electrical activity and on conditional behavior patterns. An approach to quantification of arousal studies has been made by Unna's group (306, 320). Integration of frequency and voltage of the EEG with respect to time has yielded dose-response curves which are useful only for comparisons within carefully designed similar experiments. Despite the quantitative data, results do not really separate drug effects on the RF from those at other portions of the ascending activating pathways.

One final comment is appropriate with regard to the basis for the discussion of published data reviewed in Section III: The reviewer's own bias leads to the requirements: 1) that the drug be active at doses which have for the species behavioral effects no greater than those permissible in clinical dosage; 2) reticular influences must be clearly unrelated to depression or stimulation of the circulation, temperature regulation, or respiration; 3) the magnitude of changes noted must be considered in the light of changes induced by other pharmacological agents.

III. THE INFLUENCE OF PHARMACOLOGICAL AGENTS ON THE RETICULAR FORMATION

A. Chemical mediators—endogenous compounds

Neurohumoral regulation of central nervous system activity has been postulated, debated and discussed at length in many places. Evidence for such mechanisms is usually based on analogy to the peripheral nervous system. In support of the analogy are the findings in the CNS of measurable amounts of acetylcholine, norepinephrine, and epinephrine, as well as the occurrence of synthetic and catabolic enzymes for these substances. Further, other endogenous substances have been found in brain which influence CNS activity. The role of pharmacology in examining the problem has been to test hypotheses about the neurohumoral regulation of CNS activity indirectly by altering brain levels of the various endogenous substances or the availability of postulated receptor sites. In particular, the multivariant activity of the RF has been postulated to act through endogenous neurohumoral mechanisms. This section will attempt to summarize the evidence for the hypothesis.

1. Possible cholinergic mechanisms. Following the administration of acetylcholine (ACh) (31, 39, 256, 322, 324) and the acetylcholinesterase (AChE) inhibitors, eserine (40, 121, 255, 322, 324), di*iso*propyl phosphorofluoridate (DFP) (39, 46, 322, 323, 324, 393), and tetraethylpyrophosphate (TEPP) (312), the electroencephalographic (EEG) pattern observed in unanesthetized immobilized animals was that of a "waking EEG," *i.e.*, low-voltage fast activity. Conversely (177), following treatment with atropine, trihexyphenidyl (Artane), or benztropine methane sulfonate (Cogentin), a "sleep-like," or high-voltage, slow-wave EEG

was noted as well as reversal of the cholinergic effects. Further, following these anticholinergic agents the EEG arousal response could not be elicited by stimulation of the reticular formation (50, 179). The data may be considered at first glance to support the hypothesis that cholinergic transmission is involved in the sleep-wakefulness continuum controlled by activity of the RF. However, Bradley and Elkes demonstrated (47) that injections of cholinergic agents failed to reproduce the behavioral aspects of RF stimulation, and atropine failed to produce behavioral sleep. This dissociation of EEG and behavioral responses confirmed earlier findings of Wikler in atropinized dogs (398). Moreover, severance of the brain stem at the upper end of the reticular formation failed in most investigators' hands to prevent an "EEG arousal response" to cholinergic compounds (47, 218, 286, 323) and did not prevent a reversal of the EEG effect by atropine and benztropine methane sulfonate (177, 322, 324), although the dose necessary was somewhat increased. Only Mantegazzini (271) has reported a major loss in EEG response to ACh after section of the upper pons, although Monnier (286) also found a higher dose of ACh to be required than before the section. In the isolated hemisphere preparations of Himwich and his co-workers, DFP failed to evoke arousal, suggesting a non-cortical, probably thalamic site of action (323).

Measurements of the thresholds at which stimulation of the reticular formation evokes the arousal response and elicits single responses at cortical levels offer a more direct means of evaluating the action of cholinergic agents on reticular activity. While it is true that atropine and its congeners can be shown to raise reticular formation thresholds for EEG arousal in the rabbit (177, 322, 324), cat (306, 320, 334), dog (398) and monkey (92), eserine has not been shown to affect such thresholds in rabbits (256, 286). Monnier (286) concluded that eserine acts to depress thalamocortical mechanisms instead and, additionally, acts on a general cholinergic substrate in the brain. In the reviewer's hands (218) thresholds for arousal by reticular stimulation in intact cats and in cats with lesions of the midbrain similarly failed to be altered by doses of eserine of 50 to 300 μg/kg, although Bradley (44) reported a lowering by eserine of reticular thresholds previously increased by atropine administration. Bradley found single reticular units to respond to ACh injections (43), but he concluded (44, 50) on other evidence that cholinergic receptors are not localized primarily in the RF itself and are not concerned with arousal elicited therefrom. Instead he, too, considered the receptors to be scattered diffusely through the brain. Himwich and his co-workers (177, 179, 322, 323, 324) have continued to present the view that both ascending and descending reticular influences are mediated by cholinergic mechanisms. Since they have preferred to discuss the bulbar and mesencephalic RF and the diffuse projection nuclei of the thalamus as a unitary mesodiencephalic activating system, their view is not entirely incompatible with those mentioned above. Nor does it differ too significantly from that of Rothballer (331), who has favored the viewpoint that cholinergic mechanisms may be located between the mesencephalon and the thalamus. The failure of ACh, anticholinesterase agents, and parasympathetic blocking drugs to alter *behavioral*

responses to reticular activation and their continued influence on EEG activity following midbrain section appear to be ample evidence that reticular mechanisms *per se* do not depend entirely on cholinergic transmission.

2. Possible adrenergic mechanisms. Until recently, there was much better evidence that reticular neurons are adrenergic (83, 84, 331). Alteration by injected epinephrine and norepinephrine of downstream reticular influences on motor reflex activity (85) and on cortically induced movement (352) has been noted, and these effects were shown to parallel the appearance of low-voltage, fast activity of the EEG (34, 69, 173, 272, 331). Individual reticular neurons have been found to respond to 1 to 5 μg of the compounds administered through the carotid artery irrespective of whether a blood pressure change occurred during the course of the experiment (43, 45). Cells in isolated reticular slabs were said also to be responsive (36). Careful studies (34) of animals having sections just anterior to the entrance of the fifth nerve showed epinephrine in doses as low as 5 micrograms per kilogram to produce cortical activation. On the other hand, sections just anterior to this (the *cerveau isolé* preparation) prevented the effect of injected epinephrine (34, 173).

Lesions destroying most of the RF have been shown to prevent arousal effects of epinephrine (331). Downstream effects of epinephrine on reflex activity similarly appear to depend at least in part on stimulation of the reticular formation (37). Following sections above the mesencephalon, monosynaptic reflexes were enhanced, suggesting an action on the "facilitatory area" described by Magoun; after prebulbar section, inhibition of the reflexes by epinephrine indicated unopposed activity of the brain-stem "inhibitory areas" (34, 85). Opposite actions on the linguomandibular reflex (185) are further evidence both of epinephrine effects on the RF and of the opposing RF influence on mono- and polysynaptic reflexes.

Not only can effects of stimulation of the RF be mimicked by epinephrine and norepinephrine in normal animals and those with lesions, but the compounds have been identified in the brain stem in considerable concentration (365, 380). Furthermore, both precursors and degradation products of epinephrine and norepinephrine have been shown to influence the reticular formation. Dihydroxyphenylalanine (DOPA), for example, a precursor of norepinephrine, increased arousal following reticular stimulation and enhanced cortical responses to a single shock to the reticular formation (286). A reticular action is suggested here, although some activity of the compound was retained in the *cerveau isolé* preparation, indicating additional depressant effects on medial thalamic systems. In addition, Bonvallet and her colleagues (34, 35) have suggested that although the rapid desynchronization of the EEG may be due to stimulation of the RF by neural elements, a second phase, longer lasting and slower in onset, may be due to activation of the RF by circulating epinephrine. Ingvar (195) presented evidence that direct reticular stimulation, on the other hand, releases a transmitter which activates the EEG, since isolated cortical slabs respond to brain-stem stimulation under certain conditions. Electroencephalographic arousal is accompanied by increased blood flow (199). Cross-perfusion studies (313) have confirmed Ingvar's view.

Despite these rather convincing data that adrenergic mechanisms may play a role in the effects of the RF, recent evidence has been put forth to question whether circulating adrenergic substances directly influence the brain. Weil-Malherbe *et al.* (390, 391) have found that tritiated epinephrine and norepinephrine enter the brain with difficulty, although there is a small but measurable uptake of the catecholamines in the hypothalamus. The possibility remains, therefore, that hypothalamic trigger areas sensitive to alteration of circulating adrenergic substances influence the activity of the RF. Dell (84) has recently discussed this impasse in his general review of evidence of an adrenergic mechanism of the RF.

3. Other endogenous substances. Koella *et al.* (236), on the basis of rather theoretical equations built up from experimental studies of ipsilateral and contralateral responses to drug injection, have suggested that 5-hydroxytryptamine (5-HT, serotonin) acts on the brain stem. Serotonin and 5-hydroxytryptophane (5-HTP) in low dose induced high-voltage, slow-wave activity due in part to reticular depression (286). Higher doses yielded agitation and an "arousal" response in the EEG with little influence on single potentials evoked by reticular stimulation. Since these doses are also effective in the *cerveau isolé*, there remains little direct evidence on the selective action of the compounds in the RF although they have been (365) isolated from the brain stem.

Another endogenous substance, gamma-aminobutyric acid (GABA) with possible effects on the CNS excitability (226) was found not to alter reticular mechanisms (97).

An excellent summary of humoral effects on the brain-stem RF is that of Dell (83), who concluded that effects of some of the main components of the *internal milieu* on the reticular formation "constitute one of the basic mechanisms in the translation of bodily needs into behavior." Provided one can consider only readily diffusible compounds or such substances as are released within the brain rather than non-diffusible substances in the general or cerebral circulation, Dell's summary retains interest even in the light of the work of Weil-Malherbe and his colleagues (390, 391).

B. Sedative-anesthetic agents

The sedative and anesthetic agents were the first compounds the actions of which on the RF were clearly demonstrated. In their original contribution, Moruzzi and Magoun (295) suggested the possibility that barbiturates block reticular relays. With the findings that ether and pentobarbital blocked EEG arousal by reticular stimulation and selectively depressed potentials evoked in the RF by sensory stimulation, French *et al.* (117) proposed reticular depression to be the basic mechanism of anesthesia.

The blockade by low doses of pentobarbital and ether of EEG arousal patterns, induced by sensory and reticular stimulation, was confirmed and extended by the Arduinis (13). Also in the cat, the data were confirmed by King (229, 230) and by Domino (89), and in the spinal cat by Bradley and Key (50). Larger doses of certain barbiturates have similar effects in the rabbit (132, 136) and in the rat

(333). Similar findings were made in the monkey (114, 115). The early views that selective effects were a reflection merely of the number of synaptic connections in the polyneuronal paths involved (117) were not substantiated, however, by findings that pentobarbital, thiopental, ether, and chloralose shared the ability to raise thresholds at which reticular stimulation induced EEG arousal, while the so-called specific interneuronal depressants such as mephenesin did not (89, 229, 230). Thresholds for behavioral arousal following reticular stimulation were shown to be similarly depressed in intact (222) or spinal (50) cats and monkeys (51). Generally speaking, one-third or less of the anesthetic dose was required to depress markedly the EEG (219) and behavioral responses (222) or to prevent them entirely, provided stress with concomitant epinephrine-release was avoided. Adrenalectomized animals showed increased susceptibility of "arousal responses" to barbiturates (71). The only contrary data thus far are those of Monnier (132, 136), who found that in rabbits, sedative doses (20 to 25 mg/kg) of phenobarbital failed to depress the threshold at which reticular stimulation caused EEG arousal even though these doses produced behavioral sleep. At higher doses his data are similar to those of the foregoing authors. Since as little as 1 mg/kg of pentobarbital has been reported to reduce the frequency of EEG responses in spinal cats (334), the difference may be species specific.

Considerable evidence has accumulated that reticular influences on cortical potentials (56), on spinal reflex activity (126), on recovery cycles in the thalamic relay (232), and on the conduction through the cochlear and geniculate relays (228) are reduced or blocked by barbiturates. Increases in the amplitudes of single sensory potentials in the dorsal column (153), cochlear nucleus (228), and fifth nerve nucleus (168, 170) following pentobarbital injections have been considered confirmatory evidence of influence on the RF, but are of course susceptible of other explanations. Added evidence of barbiturate effects on the RF came from Brookhart *et al.* (66) and Arduini (12, 14), who showed that slow surface negative responses (steady potentials) in the cortex following reticular stimulation were blocked by barbiturates, while similar changes in the cortex elicited by stimulating the thalamus were unaltered. The crucial findings localizing the action of these drugs to RF, however, come from studies of selective alterations in reticular activity itself. In confirmation of French *et al.* (116, 117) and the Arduinis' (13) early reports, low doses of pentobarbital have been shown to depress potentials evoked in the reticular formation by stimulation of sciatic nerves (225, 228) and by auditory stimuli (235), as well as those conducted wholely within this portion of the brain stem (156, 225, 228), although potentials can still be identified with averaging techniques (53). In these experiments simultaneous studies of a number of circuits permit ruling out generalized depressant effects.

Not only do single responses exhibit depression under barbiturate influence, but transmission of trains of impulses is even more distinctly altered. Recovery cycles of responses evoked in the RF by peripheral nerve stimulation (225, 228, 232, 378) and by local reticular stimulation (225, 228) were shown to be depressed selectively by small doses (5 to 10 mg/kg) of pentobarbital, while major sensory

paths through the lemniscus and relay nuclei of the thalamus required twice as much or more drug for similar depression (232, 273).

Responses to tooth-pulp stimulation which can be recorded in specific areas of the brain-stem reticular formation have been shown to be depressed by ether (250) and nitrous oxide (158). Similarly, the response to radial nerve stimulation was shown to be selectively depressed by ether, chloroform, divinyl ether, and trichlorethylene (80).

Studies of unit activity have also indicated the sensitivity of cells in the reticular formation to anesthetic agents (138, 339). However, inspiratory neurons were shown to fire in longer bursts, although with decreased frequency, after pentobarbital (65). Although occasional resistant circuits have been reported (138), barbiturates and ether generally depress activity of individual cells recorded with microelectrodes.

Some long-latency potentials have been demonstrated to occur in the RF under anesthesia (53, 103), but these appear after potentials normally carried by the collaterals have been depressed and may represent a secondary response of some type.

The depressant effects of thiopental have been used as a tool in the study of the RF by Magni *et al.* (260) who demonstrated that minute doses injected selectively into the lower brain stem are capable of causing EEG arousal responses. In these beautiful studies, accompanying evidence of depression of most individual units suggested that an area of the lower medulla exerts a synchronizing influence on the cortex which is normally masked by more easily analyzed major influences for arousal (see Section I, D1). This area, like the rest of the reticular formation, is depressed by barbiturates, and such selective depression may explain early desynchronization following gaseous anesthetics that Rossi and Zirondoli (330) attributed to stimulation of the RF just craniad to the trigeminal root.

So repeatable has the barbiturate depression of reticular activity been from species to species that in numerous studies pentobarbital and, less often, thiopental have become the standards of comparison for the study of other depressant drugs. There appear to be only a few reports which do not agree with the general thesis that sedation and later loss of consciousness during anesthesia result from selective depression of the RF. Two major findings following barbiturate injection led Longo and Silvestrini (257) to postulate that the anesthetic state is not necessarily related to reticular depression: loss of the EEG arousal response before the evoked RF response to sciatic stimulation, and blockade of reticular responses while cortical EEG desynchronization was still in evidence. However, their data are susceptible to the opposite interpretation, since no behavioral measurements were made and, as pointed out earlier, in the presence of drugs EEG activity need not necessarily reflect the level of consciousness.

Gangloff and Monnier (132, 136) have suggested that phenobarbital depresses the recruiting response by an action in thalamocortical circuits before altering reticular activity in the rabbit. But the conflicting evidence in the cat with both pentobarbital and thiopental (89, 229, 230) has been reported. Sites of action of

the anesthetics in addition to the RF, however, have been shown by a variety of reports. The fact that the RF is the site common to the whole series of anesthetics forms the basis of the view that anesthetic properties of the compounds are dependent at least in part on depression of this region.

C. Phenothiazines and Rauwolfia alkaloids

Because sedation and depression of motor activity were predominant characteristic actions of chlorpromazine and reserpine, it was at first postulated that the brain-stem RF might be selectively depressed. However, there is still considerable disagreement in the evidence regarding this hypothesis. Furthermore, compounds in this group were rapidly recognized to differ one from the other, hence evidence regarding a possible reticular site of action will be considered separately for each.

Chlorpromazine. The central actions of 2-chloro-10-(3-dimethylaminopropyl)-phenothiazine HCl (chlorpromazine HCl, CPZ) have been reviewed briefly by the present author (217) and extensively in a number of reports, the most recent of which is that of Dasgupta (77). Chlorpromazine has antiemetic properties which are quite clearly exerted on the so-called chemoreceptor trigger zone for emesis, which is located in the medulla, contiguous with the RF. The drug inhibits apomorphine-induced (41, 52, 141) and hydergine-induced (52, 141) emesis, presumably by a direct depression of the chemoreceptor trigger zone, upon which these emetics have been shown to act (141, 386). Unequal blockade of emesis induced by other agents led Glaviano and Wang (141) to suggest that CPZ competes at the chemoreceptor trigger zone for a receptor substance, and that its relative affinity for the hypothetical substance determines the effectiveness of blockade.

Direct effects of low doses of CPZ on vasopressor areas in the medullary brain stem have been demonstrated in decorticate cats, and of slightly higher doses in anesthetized animals (78). Martin and Eades (275) reported CPZ to depress descending RF influence on the vasomotor systems. These depressant actions may not be central, however, since in curarized cats selective depression of vasopressor areas could not be demonstrated in the absence of blockade of vasopressor responses to splanchnic stimulation (151). Thus, autonomic reflex mechanisms of the intact brain stem appear to be relatively resistant to the drug given peripherally provided there is no central depression or loss of normal input from rostral structures. Blockade of the vasopressor response to occlusion of both carotid arteries by CPZ injected intracisternally (78) at doses failing to give peripheral effects may be non-specific, in view of the local anesthetic properties of the drug (93).

The data concerning effects on the spontaneous EEG which are used as indications of the level of RF activity are not in agreement. Increased slow-wave and spindle activity in the spontaneous EEG following 2 to 5 mg/kg in the rabbit (134, 253, 254, 283, 289, 372), and slight increase in amplitude, particularly of alpha activity, in man (182) and monkey (75) were reported. In the curarized cat, 8 to 12 per sec bursts and 6 to 8 per sec slow waves were reported at 1 to 10

mg/kg (172, 274), although "transient activation periods" in one third of the animals were noted (274). Cats with chronically implanted electrodes without curarization or central anesthesia have also been reported to show similar EEG patterns with 2 to 4 mg/kg (44, 47, 49), although spontaneous alerting was demonstrated at 1 mg/kg or less (44). Mesencephalic section prevented the latter EEG changes (49). Ingvar and Soderberg (198) found a fall in cerebral vascular resistance following 1 mg/kg CPZ in normal cats but not in decerebrate cats and suggested that slow waves may be due to circulatory failure.

More direct evidence concerning possible effects of CPZ on reticular arousal mechanisms is also inconclusive. Marked blockade of EEG arousal responses to afferent stimuli, presumably by blockade of collaterals to the RF following CPZ, has also been demonstrated in the rabbit (134, 178, 283, 289) and in the cat following 2 to 4 mg/kg, i.v., but only after enormous doses intraperitoneally, *i.e.*, 15 to 20 mg/kg (49). At 30 mg/kg, responses to painful stimulation have been shown to be prevented (374).

The influence of CPZ on the EEG arousal response induced by direct stimulation of the RF has been studied using two approaches: 1) with a constant stimulus, the duration of desynchronization, changes in magnitude and frequency of the cortical activity during EEG arousal, or both, are measured, or 2) changes in the thresholds of stimulation are observed. With the former method, Martin *et al.* (274) reported that 5 to 10 mg/kg CPZ reduced the duration of, or blocked completely or both, the EEG arousal in the cat following direct stimulation of the RF. Longo *et al.* (254) reported similar blockade of response to reticular stimulation in rabbits. The simultaneous epinephrine infusions employed in the latter experiments make interpretation difficult. Rinaldi and Himwich (324) also reported reduced duration of EEG arousal in the rabbit. Studies of thresholds at which stimulation of the RF induced the EEG arousal response have permitted comparisons between drugs. Chlorpromazine was reported to depress reticular mechanisms at 3 to 6 mg/kg in the rabbit (324) and in the rat (19), but higher doses, 15 to 20 mg/kg, have opposite effects (324).

Other investigators have reported similar experiments in which the changes in the magnitude of response have been either inconsistent or of low magnitude compared to the effects of equally sedative doses of barbiturates. Electroencephalographic changes were either absent or unimpressive in man at 25 mg/kg (349), 50 mg/kg (293), and even 500 mg given chronically (142). Nor could the reviewer find consistent changes following doses up to 8 mg/kg in acute (219) or chronic cats (222) in which normal control variations in EEG had been studied over a long period and background activity was generally maintained without new environmental stimuli. Ten mg/kg seemed to be required for even slight EEG effects (221). Kaelber and Correll (212) failed to show depression of ongoing reticular activity following doses as high as 35 mg/kg, and Romagnoli (327) saw changes in the direction of high-voltage waves in dog only at 30 mg/kg.

The threshold at which stimulation of mixed afferent fibers (sciatic nerve) elicits EEG arousal presumably *via* RF pathways was shown to be only slightly raised in the cat, but the duration of arousal was shortened to little longer than

the stimulus period (219). Studies of RF thresholds to direct stimulation revealed slight falls in threshold for EEG arousal at doses under 0.3 mg/kg (50), and only slight rises in threshold at 3 to 4 mg/kg in curarized and non-curarized cats (50, 219, 311) or no effect at all (370). A comparison of effects of 3 to 5 mg/kg of barbiturate on thresholds at which reticular formation stimulation induces the EEG arousal showed that this dose induced changes of 2 to 6 volts as opposed to 0.3 to 1 volt with 5 mg/kg CPZ (50, 219, 311). Slightly larger amounts of barbiturate, though still below the anesthetic dose, raised thresholds above measurable levels. At 5 to 10 mg/kg CPZ in rabbits, Monnier and Krupp (283, 289) again showed only a shortening of the EEG arousal response. The behavioral and electrical arousal responses following RF stimulation were not differentially affected by CPZ (222).

There is good evidence of central adrenergic blocking activity of CPZ. The original observation of Hiebel *et al.* (172) that EEG activation following injected epinephrine was depressed or blocked by CPZ has been confirmed by Martin *et al.* (274). Thus, the shortening of the EEG arousal response by CPZ may represent a central adrenergic blockade in brain areas other than the RF itself, since the long-lasting phase of the arousal response has been shown to be related to release of some adrenergic substance following reticular stimulation (196, 313). It has been suggested that the intercalary cortical neurons in reverberating chains are more susceptible than RF neurons to CPZ since cortically induced seizures are shortened more than those induced by RF stimulation (240).

Drug effects on the amplitudes of responses evoked in the RF have also been inconsistent. Carreras and Angeleri (70) reported a depression of responses evoked in the brain stem by acoustic stimuli. The firing of single units in the RF following afferent stimuli was reported to be reduced by CPZ (44) provided, according to the author, "environmental type stimuli" were used. The complex CPZ effects on interaction patterns reported by Adey (2) generally indicate reduced unit firing but are at this point difficult to interpret, and considerably more data are required. On the other hand, stimuli to mixed nerves evoked single potentials in the anterior and posterior brain-stem reticular formation, which were enhanced by low doses of the drug (49, 87, 221, 225, 228). Careful histological controls (225, 228) revealed no anterior-posterior differences such as have been postulated by Martin *et al.* (274). Paired stimuli delivered at intervals of 10 to 500 msec revealed a prolongation of the recovery cycle, which was differently interpreted by the two groups reporting this finding (87, 221). The prolongation of the recovery cycle by CPZ was considered by DeMaar *et al.* (87) as indicative of depression of conduction of stimuli through the ascending reticular system. In our own studies (221), the stability of the absolute recovery period, coupled with the fact that primary responses were increased while the second potential of each pair remained at control levels, suggested that the depressed recovery-time curve was not indicative of reduced conduction of trains of impulses in the same way as that of the barbiturates, in which both first and second potentials were decreased, the second more than the first. This view is supported by findings that conduction within the RF itself was shown to be enhanced

(225, 228) by CPZ at doses of 1 to 5 mg/kg. This was confirmed by Hance (43). An alternative possibility to increased reticular formation excitability has been suggested (87), namely, that the blocking of tonic cortical and cerebellar inputs by CPZ may prevent occlusion phenomena and thus permit a larger evoked potential under the drug.

Also in contrast to reports of RF depression by CPZ at high doses, one aspect of reticular outflow activity was shown to be increased at 1 mg/kg in the cat (225, 228). The reduction in amplitude of sensory potentials at the first and second relay nuclei in the auditory pathways by stimulation of the RF was shown to be evoked at a lower threshold, and to be of longer duration following injection of the drug. The data fit with the finding (216) that CPZ, at 5 to 10 mg/kg, i.p., simulated the phenomenon associated with habituation to a wide range of stimuli. This reduction in response to incoming signals has been discussed earlier and shown to be a function of reticular activity.

The few reports on the effects of CPZ on reticular influences on motor activity do not agree. Despite early studies which failed to demonstrate an effect of CPZ on spinal reflexes (311), others (79, 241) reported them depressed even with low doses. The depression was abolished by section at the second thoracic (371) or first cervical (184, 355) segment, and hence suggested the possibility of an action on the RF. Since either inhibitory or facilitatory areas might play a role, these data do not distinguish facilitatory effects on the former from inhibitory action on the latter. The report by Kruglov (242) that CPZ and mepazine do depress both inhibition and facilitation of the patellar reflex induced by stimulation of differing RF sites requires confirmation, since the RF stimulus was monopolar and thus not localized.

No biochemical evidence of selectivity in the RF has been adduced. Grenell (149) suggested that ATP levels are altered by CPZ in the hypothalamus with little effect at lower brain-stem levels.

Compounds closely related to CPZ chemically have been studied in comparison to CPZ itself in a few investigations. No evidence of differences except in potency has been given. In view of the still unsettled questions regarding CPZ upon which so much evidence is accumulated, the data will not be reviewed in detail. Drugs tested include promazine (51, 142, 274), methopromazine (49), promethazine (Phenergan) (178, 179, 194), acepromazine (51), levomepromazine (253), prochlorpemazine (253), chlorpromazine sulfoxide (274), and the methyl and bromo derivatives of chlorpromazine (274).

Several views of the action of chlorpromazine in the central nervous system have emerged. Bovet, Longo and Silvestrini (40), DeMaar, Martin and Unna (87, 274), and Hiebel, Bonvallet and Dell (172) have concluded that a primary effect is the depression of the RF itself. Dasgupta (76, 77) has generalized the depressive effects to a mesodiencephalic system composed of reticular formation and diffuse thalamic projection system, and perhaps even including the posterior hypothalamus; Himwich and Rinaldi (174, 178, 323) have held a similar view for low doses of the drug, although they found high doses to have stimulating effects on the same structures. The French workers (86, 172) emphasized the

importance of blockade of the central effects of circulating epinephrine on the RF as the mechanism of depression, with concomitant depression of collateral afferent inflow and unmasking of sinocarotid inhibitory inflows. Bradley *et al.* (44, 47, 49, 50, 51) considered the blockade of collateral afferent excitation of the RF to be a major factor in reducing arousal responses under CPZ, particularly of those afferents carrying environmental stimuli. Gangloff, Krupp and Monnier (283, 288, 289) considered CPZ's inhibitory effects on the RF, even in the rabbit, to be minor, and perhaps preceded by transitory excitation. They conceived of the drug's major action as stimulation of thalamic pathways. Werner (392) also considered that the drug's action cannot be primarily reticular.

One source of the differing opinions may be species difference. Rodents appear generally to show greater and more consistent evidence of RF depression than do felines. Available clinical evidence that drugs inducing sleep in man can be shown to be quite selective depressants for the RF suggests that the failure of CPZ specifically to induce sleep or anesthesia in man may indicate a relative resistance of reticular mechanisms, more like the feline than the rodent.

Much more important sources of the disagreement, however, are the fundamental differences in approach and interpretation of findings. The reviewer's own bias, discussed in part above (p. 188), leads her to consider in reviewing this evidence the matter of relative dose for the species, and the magnitude and constancy of changes induced by CPZ relative to changes induced by other compounds. On these grounds and, on the basis of data from our laboratories as well, the reviewer considers that the evidence is unconvincing that chlorpromazine *exerts its tranquilizing action* by depression of the RF itself or of its responses to incoming information. The reviewer leans toward the view that at least in one aspect CPZ increases responsiveness and functional output of the RF in the dose range useful clinically: the blockade of arousal by auditory but not by "painful" or mixed afferent nerve stimulation might be related to an enhanced reticular "clamping" or "filtering" effect on afferent input to the brain in general. It is considered possible that humoral excitation of the cortex might be blocked by a adrenergic blockade at the cortex rather than within the RF. On the other hand it seems possible that separable functional units within the reticular formation may have to be separately considered. Evidence of a greater sensitivity to CPZ of thresholds for EEG arousal at rostral sites than at those more caudal in the RF supports this possibility (274), although careful histological comparisons will have to be made of electrode placements in such studies.

Reserpine. Reserpine and its congeners have been the subject of several conferences and reviews (24, 25, 217).

In contrast to chlorpromazine, the action of which on the RF has been subject to such differences of opinion, most data on reserpine have tended to indicate stimulatory effects on the RF. Early evidence emphasized that acutely administered reserpine did not induce ganglionic blockade, peripheral or central adrenergic blockade, or direct vasodilation (25, 343). Interpretations of drug activity must now be revised in view of current data indicating marked depletion of peripheral norepinephrine stores (302a).

Centrally mediated cardiovascular reflexes have been shown to be inhibited (24, 25, 217), and these pathways often involve the RF. However, there appears to be evidence that vasomotor centers in the brain-stem RF itself are not directly depressed. Reports (183) that in the anesthetized cat reserpine blocked blood pressure rises following stimulation of medullary vasomotor centers are at variance with the reviewer's (151) for unanesthetized cats. Doses of reserpine up to 1 mg/kg failed to alter medullary and mesencephalic RF thresholds for pressor responses unless the response to splanchnic stimulation was also eliminated. The hypotensive effect therefore cannot be separated from a peripheral action of the drug. The high doses (1 to 4 mg/kg) used by Bhargava and Borison (29) undoubtedly involved peripheral depression, and may certainly have induced toxicological effects, since 100 μg or less represents a severely depressant dose for the cat in terms of behavior and is accompanied by peripheral autonomic disturbances. The general toxicity of such doses has recently been emphasized (401a). This view is further supported by the finding that reserpine failed to antagonize the blood pressure rises in response to elevated intracranial pressure (317), a procedure considered to stimulate the vasomotor centers of the reticular formation. Even more striking was the failure of intracisternally injected reserpine to alter blood pressure in decerebrate cats, when equal doses by the same route in normal cats lowered blood pressure markedly. These data suggest a site of action above the midbrain (317). Bein (24) has therefore postulated that reserpine may activate a rostrally located mechanism which inhibits the brain-stem vasomotor centers rather than act on the RF directly. There appears to be similar evidence that reserpine fails to affect directly the respiratory centers of the RF (26), and that apomorphine-induced vomiting may be depressed by an action on brain-stem mechanisms for emesis (42).

Effects of reserpine on arousal mechanisms of the RF are not striking. Electroencephalographic patterns in man have been reported to be unchanged (15, 88, 152, 293), while in monkeys only a slight fall in frequency was reported (342), and cats also showed little change (219, 222). In the rabbit, a shift toward the activated EEG pattern was noted, *i.e.*, low-voltage, fast activity (321, 324, 373). Delayed slow waves and "clinical sedation" were reported (144), especially if the environment was quiet and controlled (373). Neither threshold nor duration of EEG and behavioral arousal responses to direct stimulation of the RF was altered by doses up to 100 μg/kg in the cat (219, 222). In cats, thresholds for arousal to auditory stimuli were elevated while other modalities were unaffected (50, 51). In the rabbit, however, Rinaldi and Himwich (321, 323) noted a prolongation of arousal responses to afferent stimuli and even a lowering of the reticular thresholds at 1 mg/kg. This finding is at variance with data (19) that inflow systems to the RF in the rat are depressed by reserpine. Reactivity to external stimuli in rabbits was reduced along with the cortical response to single shocks delivered to the RF (288). Monnier concluded that these apparently result from depression in thalamocortical projections rather than in the RF itself (289); the latter may be activated (288). The stimulating action of reserpine may be expressed in the parkinsonian-like syndrome reported as a side-effect

in patients and produced experimentally in the monkey by 200 to 400 μg per day (401). If this is the case, the cat may be particularly resistant to this phase of reticular action, although behavioral depression and severe autonomic manifestations are produced by reserpine at doses failing to show facilitation of RF arousal mechanisms (222).

There is a considerable literature on a possible biochemical explanation of reserpine action, much of which is reviewed elsewhere (25, 64, 217), but thus far such mechanisms have not been localized in the brain to a specific area such as the RF. This area is particularly difficult to study by sampling techniques in view of its diffuse structure and the critical importance of certain aggregates such as the vasomotor and respiratory centers. Pletscher *et al.* (309) have reported a greater concentration of serotonin in the brain stem than in the remainder of the brain and therefore a greater absolute quantity released after injection of 250 μg of reserpine in the rabbit. Brodie *et al.* (64) seem convinced that release of serotonin results from an inability of tissue to bind certain amines and is the basis of the sedative effects of the *Rauwolfia* alkaloids; however, the data thus far are not conclusive that such selective effects operate in the brain stem, or even of how important the serotonin level is to brain activity. Data on norepinephrine release at peripheral sites seem reliable, but again there is no evidence that there is a central action, or, if central, that it is peculiar to the RF. The presence of adrenergic compounds in the brain stem has been discussed earlier (p. 190).

Some reports of actions of other *Rauwolfia* alkaloids are to be found but few data are available on actions in the RF. Rescinnamine has been said to show none of the low-voltage, fast activity in the EEG of rabbits which has been reported to follow reserpine administration (341). In cats, EEG fast activity without changes in reticular thresholds for EEG arousal has been shown to follow rescinnamine and deserpidine (51); antagonism of EEG and behavioral effects of amphetamine and caffeine was also noted (341).

D. Miscellaneous sedative agents

Azacyclonol (gamma isomer of pipradrol). This compound has been reported either to have no effects on the EEG or to induce slow waves and spindles in the EEG of the rabbit (325). However, the RAS was unaltered except in almost lethal doses (*ibid.*).

Glutethimide. At 5 to 20 mg/kg, glutethimide elevated the threshold for EEG arousal by reticular stimulation and reduced the duration of response in cats (351).

Hydroxyzine. Ten to 20 mg of this compound also induces EEG synchrony and shortens the EEG arousal response to sensory stimulation (40, 51). Subcortical structures show increased excitability in the rabbit (40), while 2 to 4 mg/kg blocks arousal due to auditory stimulation in the cat (51). However, a reduced duration of EEG arousal following direct reticular stimulation in the rabbit (353) and cat (51) has been reported. In the latter species, the dose required was 2 to 3 times that causing depression of the EEG response to auditory stimuli.

Methaminodiazepoxide. One of the newer depressants with "taming effects"

(316) has been shown to block the EEG arousal response to direct reticular stimulation, but relatively high doses are required (315).

Methylprylon and hydroxydione. At 5 to 10 mg/kg in cats, methylprylon had effects similar to those of glutethimide (351), and depression of "alerting" was described in dogs (335). Similar data with hydroxydione were reported at 5 to 40 mg/kg by Sigg (351).

E. Muscle relaxants

Mephenesin, prenderol, benzothiazoles, and benzoxazoles. Early studies of the so-called interneuron depressants were suggestive of supraspinal activity in the region of the RF (211). Mephenesin, prenderol, and the benzothiazoles were shown to inhibit descending reticular facilitatory and inhibitory influences on reflex activity not only at spinal levels (123, 124, 162) but through the brain stem (233). It was tempting to suggest on the basis of these and other reports (404) that inhibition of reticular pathways, presumably rich in interneuronal connections, was a major action of these agents. Newer anatomical information (*cf.* Section I, p. 177) failed to support this hypothesis. Decisive experiments showed EEG arousal responses induced by stimulation of the RF to be untouched by mephenesin (89, 229, 230) and the benzothiazoles (229, 230), and these data supported physiological evidence (366) of the presence of reticulo-cortical pathways outside the diffuse thalamic projection system. Stimulatory effects of prenderol above the cord (124) illustrate how critically drug studies must be evaluated when they are based on alterations in the efferent functions of the RF. Zoxazolamine (2-amino-5-chlorobenzoxazole) has been reported (in abstract) (125) to reduce cortical response to reticular stimulation, but the foregoing evidence and that on actions of meprobamate and phenaglycodol (see below) make a depressant action of this compound directly on the RF seem unlikely.

Meprobamate, phenaglycodol, and carisoprodol. These compounds possess certain clinical resemblances to barbiturates and some "tranquilizing" activity like that of the chlorpromazine series, as well as "interneuron depressant" properties like those of mephenesin. They fit with difficulty into each of these classes and are therefore discussed separately. At higher dose levels, meprobamate and phenaglycodol produce predominantly barbiturate-like effects on behavior, but at doses closer to those used clinically there is little evidence of a selective reticular depression like that produced by barbiturates (130). Early studies suggested a thalamic locus of action of meprobamate (27, 159, 160). Phenaglycodol was first reported because of its effects on polysynaptic spinal pathways (356). Bovet (40) reported a shortening of EEG arousal to acoustic stimuli and a slow wave, high-voltage type of EEG following meprobamate in the rabbit. In the cat the elevation of the auditory threshold was considered to result from "habituation" (51), in view of negative data on RF thresholds. A careful comparison of the agents on EEG arousal pathways of normal cats and of those with lesions (130) demonstrated somewhat enhanced arousal responses following both the drugs in normal animals, although the thresholds could not be demonstrably lowered. In cats with lesions in the upper brain stem, the "EEG arousal" responses were de-

pressed. Thus the primary depression of higher centers suggested by Hendley (159, 160) and by Mercier and Dessaigne (280) may be masked by concomitant drug stimulation of the RF. Evidence in favor of this hypothesis for meprobamate comes from the lack of direct EEG effect of 20 to 40 mg/kg, a dose causing depression of recruiting in intact animals but not in animals with lesions which block the ascending reticular influences on the recruiting response (130). In the case of phenaglycodol at 10 to 20 mg/kg, the reticular stimulation may act to counterbalance a depression of thalamo-cortical mechanisms, since enhanced recruitment is noted in animals with lesions but not if the RF is intact. In intact animals slow, high-voltage activity is induced in the EEG by these doses (*ibid.*). Kletzkin and Berger (234) confirmed the finding that activation patterns in the EEG following RF stimulation were not depressed by meprobamate in the cat although they did not report the slight increase in qualitative signs of stimulation described by Gangloff (130). Potentials evoked within the reticular formation by acoustic stimuli were unaltered by 40 mg/kg meprobamate in the cat, and enhanced reticular responsiveness was demonstrated at 80 mg/kg (235). Of some possible connection are the independent comments of Unna, Irwin, and Pfeiffer that they had noted meprobamate had locomotor stimulant properties (307, Discussion). These data, along with those of Kletzkin and Berger, would fit with enhanced rather than depressed reticular activity.

The *iso*propyl derivative of meprobamate, carisoprodol, has been reported to share the muscle relaxant properties of the parent substance but to differ in its effects on the RF (28). In cats at a dosage that produces EEG synchronization (5 to 10 mg/kg), the EEG arousal response elicited by stimulation of the nucleus centralis lateralis of the thalamus, the mesencephalic RF, or the sciatic nerve was blocked; this was also true in the rabbit (252). Since these doses had not produced behavioral sedation in intact animals, Berger *et al.* (28) have interpreted the findings to indicate a dissociation of EEG activity and behavior similar to that observed with atropine, but they have presented no direct evidence as yet.

F. Stimulants

1. Psychomotor stimulants. The amphetamine-like compounds have repeatedly been demonstrated to induce low-voltage, fast activity in the EEG and behavioral awakening. Several reviews have surveyed the extensive literature (175, 376).

Amphetamine. At doses of 0.5 to 1.0 mg/kg, amphetamine has been shown to produce the "arousal" type of EEG in rabbits (255, 256, 283, 324) and in cats (47, 68, 69, 173, 218) and to produce behavioral evidence of arousal (47). Hiebel *et al.* (173) were among the first to suggest that this effect resulted from direct stimulation of the RF. Other data suggested that such stimulation also simultaneously activates downflow influences on motor activity in decerebrate rabbits (255). Evidence of an action of amphetamine directly on the RF came from the failure of the compound to activate the EEG at all when lesions of the midbrain destroyed most of the mesencephalic RF (218) or interrupted its pathways to the cortex (47, 173). High spinal section (47, 334) or midbrain section leaving

much of the mesencephalon intact (173, 255) did not prevent the EEG desynchronization following the drug. Behavioral arousal induced by amphetamine persisted even when EEG desynchrony was overcome by atropine administration (44). Such data confirm the view that pharmacological separation of EEG and behavioral arousal is possible and emphasize the need for caution in interpretation of changes in electrical activity alone.

The effectiveness of sensory stimulation in causing EEG arousal has been shown to be increased by 0.5 mg/kg in the cat (50) and in the rabbit at 3 mg/kg (324). Himwich (175) considered this as evidence that adrenergic compounds act to increase sensory input from the autonomic pathways rather than to exert a direct reticular action. In view of the desynchrony of the EEG it is difficult to obtain direct evidence on this point by measurement of thresholds at which stimulation of the RF itself will induce arousal. However, a number of investigators have been able to show some lowering of the reticular thresholds (50, 218, 283), although Longo and Silvestrini (255) could not obtain this effect in rabbits. A prompt reversal of effects of low doses of barbiturates on reticular thresholds has been shown to follow 1 mg/kg of amphetamine in the cat (218), but the effects of higher doses of barbiturates are not antagonized (44). The effectiveness of amphetamine in lowering the threshold at which stimulation of the mesencephalic RF induces EEG arousal has been dramatically demonstrated in animals having bilateral lesions in the RF at the level of the superior colliculus. In these animals administration of *d*-amphetamine in doses up to 15 mg/kg did not cause spontaneous low-voltage, fast activity in the EEG. Thresholds for EEG arousal could thus be accurately measured at points in the RF rostral to the lesion. These were lowered by 0.5 to 1 mg/kg of the drug (218).

In the light of the foregoing findings, it does not as yet seem possible to interpret Hance's report (156) that amphetamine reduces the amplitude of potentials recorded within the central gray following stimulation of the caudal reticular formation. Nor does failure of amphetamine to increase reticular unit firing seem compatible with other evidence (340), but the difficulty of demonstrating generalized pharmacological effects with unit studies is often one of limited sampling of the neural population.

Effects of amphetamine do not seem to be related to blood pressure changes (47). Although Ingvar (196) found increased cerebral blood flow, there was no evidence that this initiated arousal; Kety (215) concluded that total cerebral circulation had not been shown to be altered in man.

Pipradrol has also been shown to increase the response of the EEG to sensory and to RF stimulation at 0.5 to 3 mg/kg in the rabbit and to cause continuous alerting at 3 to 6 mg/kg (324).

Methylphenidate (*Ritalin*) was reported to cause activating effects on the EEG similar to those of reticular stimulation at 1 mg/kg in the rabbit (175). This effect could be abolished at least in the cat by destruction of the posterior diencephalon (205). While these data are suggestive of an action on mesencephalic RF activity, direct evidence is still lacking.

Caffeine similarly appears to cause EEG arousal in the cat (204, 334) and in

the rabbit (243), but it is not clear how dependent this action is on effects in the RF itself. Potentials evoked within the brain stem by click were enhanced following 15 mg/kg of the drug in the cat but only after decerebration. Direct activation of the EEG by caffeine remained possible after midbrain or diencephalic lesions (204, 243), and even a direct action on the isolated cortical slab was observed (204). Since the histological limits of the lesions were not described, however, the reviewer cannot compare these data with those on amphetamine in which the amount of remaining RF tissue is critical to the persistence of drug effect. In the rabbit, changes in RF thresholds for arousal have not been demonstrated following caffeine (243). There is thus no adequate evidence at present of a reticular site of action for the drug.

Dimethylaminoethanol. Peculiarly equivocal data on central actions of dimethylaminoethanol have been obtained. Studies by the author and colleagues (218) designed to compare drug effects on EEG arousal patterns evoked by stimulation of peripheral nerve, the bulbar and mesencephalic RF, and central thalamic nuclei revealed that in certain cats 5 to 20 mg/kg lowered thresholds at which EEG arousal could be induced and also induced spontaneous arousal patterns in cortical EEG's. A direct antagonism of barbiturate effects on reticular thresholds could be demonstrated. However, in other animals if low doses were ineffective, amounts up to 250 mg/kg could be added without action, suggesting that perhaps a particular biochemical balance is necessary for the effect of the drug. Although the thresholds at which the diffuse thalamic projection system could induce arousal were altered along with reticular thresholds in some cases, studies of cats with midbrain lesions showed that tonic activity of the thalamus alone could not maintain or initiate EEG arousal patterns in the absence of the ascending reticular influences. The authors therefore concluded that, when effective, dimethylaminoethanol probably acts by stimulation of the RF and thus resembles amphetamine rather than eserine or the cholinergic drugs which do not require reticulocortical connections for their activity. Goldstein, on the other hand, using EEG analyses alone in the rabbit, found that 5 mg/kg of dimethylaminoethanol induced hypersynchrony of the EEG alone with behavioral effects considered to be excitant (143). Whether individual differences between animals were striking in his studies was not discussed.

2. Convulsants. Localization of the actions of pentylenetetrazol, picrotoxin, bemegride (Megimide), and thiosemicarbazide at the RF has not been demonstrable. Hahn (154) in a recent review has summarized the data on analeptics regarding both site and mode of action. Despite reports (374) that pentylenetetrazol alters the normal balance between influences of the RF and diffuse thalamic projection system on cortical mechanisms, and that it augments the amplitude and duration of potentials invoked in the RF by click (13), Hahn concluded that pentylenetetrazol owes its action to generalized stimulation rather than to a selective action on reticular mechanisms. The possibility exists that the intensity and persistence of the induced convulsive pattern depend on the integrity of reticular connections (107), but such data are not evidence of a drug action on the RF itself. In fact, results obtained by close-arterial injection

techniques have indicated that in rabbits, at least, the medulla and pons are less sensitive to pentylenetetrazol than are higher centers (202). No selectivity was demonstrated with picrotoxin or nikethamide (202). Localization of the earliest electrical signs of convulsive activity following thiosemicarbazide injection has suggested that the caudate nucleus and central gray first show spiking activity, with parallel biochemical changes (lowered GABA), associated with the production of the seizures (224). Although tegmental structures near the borders of the central gray were reported not to be involved (310), the biochemical changes could not be localized so closely as to exclude the nearby reticular formation (224) nor could the region of pick-up from a macroelectrode be so closely defined. While the RF thus remains a candidate as a site of action, there is no direct evidence that this convulsive agent acts on the reticular mechanisms except for a single finding indicating an enhanced RF effect on spinal reflex activity (96).

3. Miscellaneous stimulants. A special group of compounds having antidepressant effects are those currently termed "psychic energizers." These may not properly belong in the class of stimulants but are included here because of their stimulant-like effects on behavior.

Orphenadrine (Norflex) at 15 mg/kg and *imipramine* (Tofranil) at 2.5 mg/kg have been shown to block arousal due to sound and, at higher doses, to pain, in the rabbit (175). The latter also depressed EEG responses to peripheral stimuli in the cat (74). These data, as well as the finding (51) of an elevated threshold at which electrical stimulation of the RF induces arousal following the drug, would strongly suggest an activity differing from that of amphetamine. Direct measurements of RF thresholds in rabbits on the other hand showed a fall in threshold after the drug (289).

The monoamine oxidase (MAO) inhibitors *iproniazid* (Marsilid), *pheniprazine* (Catron), and *tranylcypromine* (Parnate) were reported to induce low-voltage, fast activity in the rabbit EEG (73), but no data on direct RF stimulation were reported. Other investigators (244) reported that iproniazid did not alter thresholds at which RF stimulation induced EEG arousal in the cat. *Nialamide* (Niamid) induced behavioral stimulation without concomitant EEG effects, and again reticular thresholds were unaltered (122).

The EEG desynchronization and behavioral arousal following *etryptamine* (*dl*-α-ethyltryptamine) has been shown by Matthews *et al.* (276) to be prevented by precollicular section but not by section of the cord at C-1 in the cat, indicating an effect in the brain-stem region. However, major sensory paths through the lemnisci are not involved. Himwich (176) has extended these results by comparing effects of injection of the drug into the circulation of the lower brain stem with those following injection into the cerebral circulation as a whole. He was able to distinguish two phases of the action of the compound. The initial EEG arousal was amphetamine-like and not elicitable after midpontine section if drug injection was confined to the bulbar region. The delayed "arousal" effect was related to a decrease in 5-hydroxytryptamine in the medullary region. The data on this whole group of compounds are too limited for conclusions to be drawn as to their possible effects on the RF except in the case of etryptamine, and the

evidence regarding the latter suggests that most probably reticular actions are not related to MAO inhibition.

G. Hallucinogenic drugs

The psychotomimetic or hallucinogenic drugs (LSD-25, mescaline and a host of newer agents) have been studied both independently and as antagonists of agents helpful in treating experimental or clinical psychotic episodes. There are great species differences with respect to effects in man and other animals. Furthermore, the question is not yet settled as to whether psychotherapeutic agents act on the RF and, if they do, whether all act similarly (see Section IIIC). Thus, studies of antagonisms of EEG effects on psychotherapeutic drugs by hallucinogens or *vice versa* do not contribute to localization of sites of action of either. A review of the major neurophysiological findings and clinical EEG data has been given by Evarts (101), who has included a review of data on combination and antagonistic effects.

In brief, available evidence indicates that while LSD-25 may be seen to increase incidence of low-voltage, fast activity of the EEG in the rabbit (82, 325), in the cat (47, 102, 345), and sometimes in man (101), 100 to 200 μg/kg in the cat (304) and 20 to 60 μg/kg in the rabbit (325) have been reported to induce slow waves, or spindling, or both. The low-voltage, fast activity response to LSD-25 in low dose has to the reviewer and co-workers seemed unimpressive in the cat (223). Attempts to localize the source of the EEG effect by lesions at various brain-stem levels led Bradley (44) to conclude that the presence of afferent inflow from spinal levels is critical to an LSD-25 effect on the EEG. The findings of Rinaldi *et al.* (325) that thresholds at which stimulation of the RF yields arousal are reduced by 1 to 5 μg/kg in rabbits and increased at larger doses (20 to 60 μg/kg) may contrast with ours (223), that LSD-25 has little or no action in the cat up to 100 μg/kg, because of differing levels of afferent input to the brain under the conditions of the two experiments. In line with this view are the differing findings that LSD-25 at 1 to 32 μg/kg in the cat enhanced reticuloreticular conduction if it acted at all (156) and lowered the threshold at which auditory stimuli caused arousal at a dose which induced no change in thresholds for direct stimulation of the RF (50). Cortical responses to single stimuli to the RF were enhanced by LSD-25 in the rabbit (290, 292). Homolateral effects of LSD-25 when injected into the carotid artery also mitigate against the brain stem as an important site of action of the drug (197). Furthermore, intraventricular injection of doses up to 800 mg is not followed by changes in reticular thresholds for EEG arousal (381).

Mescaline was reported to be similar to LSD-25 if given intraventricularly in the rabbit (325), although Schwartz (345) reported spiking and slow waves in the cat after intraventricular injection. *Adrenochrome* has been shown to increase low-voltage activity in the EEG of rabbits at 5 mg/kg, which is only partly prevented by the *cerveau isolé* lesion (291), but intraventricular injection induces 4 per second activity in the cat (345). Increased ability of the mesencephalic RF to cause the "arousal reaction" in the EEG, and increased amplitude of cortical responses to reticular stimulation were demonstrated (291).

Attempts to study the effects of intraventricularly injected 5-hydroxytryptophane against LSD-25, mescaline, adrenochrome, or *adrenolutin* on the EEG and behavior in conscious cats led to very equivocal results. There was no consistent antagonism or consistent pattern of EEG change between drugs (345). Serotonin enhanced rather than antagonized high-amplitude, slow activity induced in the EEG by intraventricular LSD-25 (48). *Psilocybin* was reported to cause EEG and behavioral activation in the rabbit (284), but since cortical responses to RF stimulation were unchanged, Monnier concluded that this hallucinogen probably acts on thalamic systems. *Ibogaine* was also reported to stimulate EEG activation responses (344), but the data are not sufficient to implicate the RF as the site of action. *Bulbocapnine* has been said to raise seizure thresholds in the reticular formation and simultaneously to induce EEG slow activity (305).

Phenylcyclohexyl (Sernyl), despite clinical suggestions to the contrary (281), seemed not to act on the reticular formation, since drug-induced EEG alterations occurred even in isolated hemisphere and undercut cortex preparations (379). The site at which the compound induced the facilitation in corticipetal pathways from the RF noted by Adey and Dunlop (3) has not yet been clarified.

From the available evidence as reported above and in several reviews, the reviewer concurs with Purpura (314) that a direct action of LSD-25 and other hallucinogens on the brain-stem RF has not been proved. Possible actions on afferent inputs, on cortical mechanisms, or both are more likely to be the source of the hallucinogenic activity.

H. Miscellaneous centrally active compounds

1. Opioids. The actions of opioid analgesics have been extensively reviewed by Wikler (50, 59, 397, 400) and Domino (91). Specific reticular functions have been shown to be modified in a number of species. The respiratory centers have been shown to be depressed (181). On the basis of altered tonus and reflex amplitude in decorticate and decerebrate cats and in cats with high spinal sections, Wikler suggested (44, 45, 50, 395, 396, 397) that opioids directly alter interneuronal activity in the bulbar RF to produce their characteristic changes in analgesic test reflexes. General analgesia and the psychic effects are experimentally inseparable from action at all levels of integration; thus one cannot consider the opioids in any way selective for the RF.

The arousal response has been studied in a number of species. Deneau and Takaori could find no alteration in the threshold at which stimulation of the RF induced EEG arousal following 3 to 9 mg/kg morphine sulfate in the monkey [unpublished data cited by Domino (91)]. In the cat, 10 mg/kg morphine sulfate, which was followed by spontaneous behavioral and cortical EEG arousal patterns, caused little alteration in behavioral and neocortical responses to sensory stimuli or direct RF stimulation (403). These workers described some depression in simultaneous responses of the limbic system but their results are open to other interpretation, since the high-voltage, slow activity in the rhinencephalon which they ascribed to sleep had been described by Green and Arduini (148) as characteristic of arousal in that structure. However, Fujita *et al.* (119, 120) reported reticular mechanisms of EEG arousal to be depressed by morphine in the cat, as

did Sawyer *et al.* (333) for the rat. Some disagreement also exists regarding the effects of morphine on rabbits. Silvestrini and Longo (354) showed that the EEG arousal responses to pain were selectively depressed at 5 to 10 mg/kg morphine, while arousal responses to direct RF stimulations were unaltered. In contrast Gangloff and Monnier (135) found that the drug depressed respiration, cortical responses to stimuli applied to the RF at 3 per second, and the cortical arousal responses to high-frequency stimulation of the RF. Ten mg/kg levorphan had a similar effect, while levallorphan (6 to 15 mg/kg) caused reticular stimulation as evidenced by wakefulness, an EEG typical of arousal, and enhanced EEG arousal responses to direct stimulation of the RF. One finding which is not quite in keeping with the view of enhanced reticular activity following levallorphan was its failure to antagonize respiratory depression following barbiturate administration. Reticular depression from morphine and levorphan was reversed, however, by levallorphan. Gangloff and Monnier considered the data to be further evidence that barbiturates depress thalamocortical circuits despite other data to the contrary (89, 230). However, Gangloff and Monnier did not identify exactly the sites in the brain stem stimulated, and the morphine and levorphan blockade of response may be localized, for example, to pain pathways identified by Livingston's group (250). Conversely, localized RF responses to single tooth pulp stimuli were enhanced rather than depressed by morphine in the dog (161). Reticular descending influences in the cat were shown to be increased (369). Since reflexes normally inhibited by morphine are facilitated by the drug after section of the central bulbar area, Takagi assumed the facilitatory action of morphine in intact animals to be greatest in this medial posterior portion of the RF.

The opposing data both within and across species point up the crucial importance of histological controls and the need for their detailed publication in certain cases. It may be that with opioids it will be possible to identify meaningful centers of the RF the physiological differentiation of which has not thus far been possible. On the other hand, dose levels and species differences play important roles in the variability described.

2. Anticonvulsants. Investigations of possible effects of anticonvulsant drugs on the CNS have not been undertaken with special attention to the RF. The major approach has been to induce seizures by a variety of means, then test drug action on seizure activity and try to correlate certain types of experimental seizures with clinical epilepsy. Although convulsions can be evoked in the cat or rat by direct stimulation of the RF (133, 239, 287), self-sustained seizure discharges are not induced at voltages comparable to those which induce them in the rhinencephalon, diencephalon, or cortex, nor do discharges generally spread first to the reticular formation from the cortex. Rhinencephalic seizures do appear to spread first to certain areas of the RF before other sites. The areas that have been shown to be connected to the rhinencephalon most directly (4, 5, 6, 299) (near the posterior commissure, for example) show these propagated discharges most frequently. Woodbury *et al.* postulated that the RF is part of an oscillator mechanism involved in the maintenance of minimal seizure discharge

(402), but these workers have not attempted to isolate drug action on the RF itself. Published data indicate that the anticonvulsant activity of various drugs and their effects on various aspects of reticular activity appear to be unrelated. Meprobamate, for example, reduces or prevents rhinencephalic seizures, but exerts a slight facilitatory action on the RF. In contrast, barbiturates are as a class depressants of reticular activity even in low dose, but quite variable in their anticonvulsant properties (E. K. Killam, and K. F. Killam, unpublished data). Reserpine may induce rhinencephalic seizures or increase their spread into generalized convulsions (222), but this compound appears either to have no effect or slightly to stimulate the RF. The most direct reports of the actions of anticonvulsants on the RF have come from Monnier and his group, who have studied the effects of these compounds on the rabbit. In studies of seizure thresholds and duration following stimulation of the reticular formation, rhinencephalon, diencephalon, and cortex they could find no evidence of a selective action of the anticonvulsants on the RF itself (133, 287). The slight reduction in EEG arousal response to RF stimulation induced by diphenylhydantoin (244) was not controlled by simultaneous measurements in other systems and thus does not controvert the conclusions of Gangloff and Monnier.

3. Antiparkinsonian agents. Certain of the antiparkinsonian drugs have been reported to act on the RF, partly on the basis of questionable theoretical grounds, as already discussed (III A) (p. 188. If, as Ward (389) and others have proposed, parkinsonian tremor is a manifestation of excessive reticular activity related to a cholinergic sensitization phenomenon, it would be reasonable to suppose that parasympathetic blocking properties would be manifested by drugs useful in the clinic. This is indeed the case—atropine itself remains a classic antiparkinsonian drug. On the other hand, extrapolation from peripheral ACh-blocking properties to central effects on the RF is fraught with danger. It has already been pointed out (p. 188) that data suggesting activity of cholinergic compounds in the brain stem may need re-examination in the light of their failure to induce behavioral concomitants of the EEG changes. Similarly, anticholinergic drugs cannot be said to act necessarily or selectively on reticular structures despite the number of such interpretations of EEG data. Himwich (177, 178, 324) summarized findings that in rabbits benztropine methanesulfonate (Cogentin), trihexyphenidyl (Artane), diphenhydramine (Benadryl), and caramiphen (Parpanit), like N-allylnoratropine (361) and atropine itself produced high-voltage, slow waves in the EEG, blocked arousal responses to painful stimuli or to direct reticular stimulation, and prevented the EEG response to DFP, eserine, reserpine, and other compounds. Also in rabbits, scopolamine at 0.05 to 0.1 mg/kg was found to exert similar effects, but responses to "painful stimuli" were found not to be blocked (251). No effect was seen to be exerted on downflow effects of the RF on motor activity, which had been suggested as part of the antiparkinsonian activity, although blockade of descending vasomotor effects was reported (275).

Interpretations that these data indicate a reticular action have failed to account for the continued action of atropine-like agents when ascending reticular

connections are cut off by brain-stem transections. Thus, they might indicate depression in the thalamic region of the activating system rather than in the RF itself, since potentials evoked in the cortical areas involved have not been shown to be markedly altered by atropine-like drugs (157).

4. Others. Benactyzine. Production of high-voltage, slow waves in the EEG and blockade of effects of sensory stimulation have been reported following 0.05 to 1.0 mg/kg benactyzine (40). Direct studies of thresholds at which stimulation of the RF alters EEG activity have shown the compound to be capable of blocking reticular influences at 1.5 mg/kg in the rabbit (175), or at least elevating the threshold markedly (353). The frequency of the arousal response was decreased in cats (244). The behavioral aspects of arousal have been studied along with the EEG, and the former were not altered when thresholds for EEG arousal were elevated (51). These data would seem critical to the interpretation of the findings in view of the compound's peripheral atropine-like properties and of Bovet's report (40) of central atropine-like dissociation of the rostral and caudal influences of hypothalamic stimulation.

CONCLUDING REMARKS

As can be seen from this review, the present techniques in neuropharmacology do not allow us clearly to conclude that specific effects on the reticular formation of the brain represent the major mechanism of action of certain classes of compounds.

There is some indication that adrenergic transmitters may act at synapses in the RF, but the evidence is confused by the question of whether such compounds, peripherally injected, pass the blood-brain barrier to reach active sites. Cholinergic mechanisms seem less likely to be selective for the brain stem, and indeed may not operate in the RF at all. The data are too few to allow conclusions regarding other possible transmitters.

Anesthetic agents as a group can reliably be considered to exert clear depressant actions on the RF and most probably affect this region early or even at the lowest active dose. Responses to afferent stimuli are prevented or reduced, recovery time of neurons is prolonged, and outflows particularly for arousal and sensory modulation are blocked. Effects of these compounds at other CNS sites however, contribute to the state of anesthesia at least in some part.

Almost as good evidence exists that the psychomotor stimulant, amphetamine, enhances reticular activity, both increasing potentials evoked within the RF and facilitating outflow systems, especially the rostrally directed activating system for arousal. Evidence is still only suggestive for other compounds of this group, like methylphenidate, pipradrol and caffeine.

Other psychotherapeutic compounds have been subjected to much scrutiny and here opinion is divided. The reviewer considers that, at low doses, equivalent to those acceptable for out-patient therapy, depressant effects on the RF are unimportant, if they indeed exist. Chlorpromazine increases reticular reception of afferent inflow as represented by evoked potentials, and seems to enhance the RF clamping or modulation of afferent signals. It is more generally accepted

that reserpine either increases or does not alter the RF at reasonable dosage levels. Meprobamate and phenaglycodol have been suggested to exert a slight stimulatory action on the RF. Carisoprodol, however, has only been reported to block the reticular influences for arousal and seems also, like the antiparkinsonian compounds (the atropine series in particular), to disassociate behavioral and EEG evidences of the state of sleep and wakefulness.

"Interneuron depressants" such as mephenesin and the benzothiazoles and benzoxazoles, convulsants such as strychnine and pentylenetetrazol, and such stimulants as orphenadrine and imipramine have thus far been shown not to act on the RF. Data on monoamine oxidase inhibitors are too slim to allow conclusions. Etryptamine alone of the non-psychomotor stimulants may selectively stimulate the RF in an amphetamine-like manner. Hallucinogenic agents probably do not act on the RF; it is more likely that they block afferent signals before they reach the brain stem.

Some evidence of depressant effects of glutethimide, hydroxyzine, methylprylon, and hydroxydione on the RF has been presented, but it is still too meager for judgment. Opioids and anticonvulsant compounds in general may exert depressant effects on reticular neurons or synapses, but there is no evidence that the effect is selective, and differences both between species and between special anatomical areas may be important.

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