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BEHAVIORAL AND ELECTROENCEPHALOGRAPHIC EFFECTS OF ATROPINE AND RELATED COMPOUNDS

V. G. LONGO

Istituto Superiore di Sanità, Roma, Italy

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In the description of the effects of atropine and its congeners, a distinction between their peripheral and central actions has always been made. The studies have resulted in a satisfactory delineation of their peripheral effects, but this cannot be said for their central actions, because of divergent views of the importance, the nature, and even the existence of various central nervous system effects.

This review is concerned primarily with atropine and scopolamine; other anticholinergic compounds will be referred to when necessary. The effects observed in man will be reviewed in an attempt to set forth the essential and characteristic elements which make up the "central anticholinergic syndrome." In a separate chapter the electroencephalographic signs of the central action of atropine and congeners will be described. The second part of the paper will deal with the experimental studies in animals. The behavioral and electrophysiological aspects of the anticholinergic effect will be analyzed with emphasis on clarification of the sites and modes of action of the drugs.

1. EFFECTS IN MAN

A. The central anticholinergic syndrome

1. Atropine. The large amount of information that has been collected concerning the effects of atropine on human behavior is directly or indirectly related to

TABLE 1

Atropine symptomatology in man

0.5 mg	Slight cardiac slowing; some dryness of mouth; inhibition of sweating
1.0 mg	Definite dryness of mouth; thirst; acceleration of heart; sometimes preceded by slowing; mild dilatation of pupil
2.0 mg	Rapid heart rate; palpitation; marked xerostomia; dilated pupils; some blurring of near vision
5.0 mg	All of the above symptoms marked; speech disturbed; difficulty in swallowing; restlessness and fatigue; headache; dry skin; difficulty in micturition
10.0 mg and more	Above symptoms more marked; pulse rapid and weak; iris practically obliterated; vision very blurred; skin flushed, hot, dry, and scarlet; ataxia, restlessness and excitment; hallucinations and delirium; coma

From Goodman and Gilman, The Pharmacological Basis of Therapeutics, 3rd ed., The Macmillan Co., Inc., New York, 1965.

the vast clinical use of the alkaloid. Contributions have been derived from therapy-oriented investigations, from laboratory experiments, and from the observations of persons intoxicated with atropine. Table 1 lists the manifestations of increasing doses of atropine. A characteristic of the drug is the wide range between the effective and lethal doses. In fact, in this table the word "more" refers to dosage which in some cases reached up to 200 mg. Also the number of fatalities due to atropine is extremely low; a case is described of survival after ingestion of 1 g of the drug (4).

At the usual therapeutic doses, which vary between 0.5 and 2 mg, the central effects of atropine are not noticeable, with the exception of a modest stimulation of the respiratory centers. When the dosage level exceeds 10 mg, there seems to be no additional aggravation of the peripheral manifestations, whereas the central effects of the drug increase in intensity, and become the most striking aspect of the syndrome. These central effects result in a complex symptomatology that is difficult to evaluate and classify; adding to this difficulty are the complicating influences due to alterations of the peripheral, autonomic effectors. There are, however, some symptoms that have been consistently reported and which can be considered characteristic of the action of atropine; these are discussed below.

a. *Diminution of both the power of concentration and memory* has been described after doses ranging between 0.4 and 10 mg (114, 116, 127, 128, 177). A detailed analysis of this effect was carried out by Callaway and Band (25). From the influence of the drug (2 mg, intramuscularly) on performance in a battery of psychological tests these authors concluded that "broadening of attention" is the most characteristic effect of atropine.

b. *Drowsiness, withdrawal and tendency to sleep* appear regularly at doses above 2 mg (50, 116, 144, 171). Although these symptoms are intermingled with periods of apprehension, they are considered by some authors to be the predominant ones (25, 128, 177).

c. *The excitatory effect* which has often been reported will be discussed more fully because of its peculiarity. A distinction should be made between the state of apprehension that may be observed after relatively low doses (up to 10 mg)

and the state of confusion which ensues upon administration of higher doses. The central origin of the state of apprehension is at least doubtful, and several observations suggest the importance of extraneous factors (for example, the nature of the experiment, the environment, the emotional state of the subject) in determining the response observed. The symptoms of parasympathetic block (dryness of skin and mouth, blurring of vision due to pupillary dilatation and cyclopegia, tachycardia) may be so unpleasant that the restlessness and uneasiness so often described perhaps can be attributed to the discomfort resulting from the peripheral effects, rather than to a central action of atropine.

During the state of confusion after high doses of the alkaloid, some excitatory effects are noticeable. The psychic and neurological syndrome provoked by atropine was reviewed by De Boor (36). This author reported in detail observations made during accidental atropine poisoning or self-induced intoxication. In addition to the autonomic effects, hallucinations, stereotyped movements, bursts of laughter, and agitation appeared to be characteristic.

In 1950 Forrer (49) introduced treatment with large doses of atropine as a type of somatic therapy in neuropsychiatry. Forrer reported some preliminary results of "atropine toxicity therapy" brought about by the parenteral administration of 32 mg of the drug (about 50 times the customary dose); improvement was believed to occur in psychotic states of various origin. This "atropine toxicity therapy" is still in use but has undergone modifications. In an extensive report on the signs of intoxication of patients undergoing "atropine toxicity therapy" and receiving parenterally 50 to 200 mg of the alkaloid, Miller (116) made an observation of considerable significance with respect to the somatic symptoms of excitation. "Signs attributable to the central effects of the drug include restlessness, excitment, confusion, weakness, giddiness, muscular incoordination and speech disturbance. Nausea and occasionally vomiting also may occur. The clinical picture is one of an acute brain syndrome in which memory is disturbed, orientation faulty and in which illusions and hallucinations, frequently visual, are common. The sensorium is clouded and delirium proceeds to coma. In contrast to what might be expected, the restlessness, excitement, confusion, etc. do not usually give rise to behavioral disorder. Patients pass through these phases in a fairly comfortable state, and only rarely has there been occurrence of aggressive or disturbed behavior. Invariably, a few kind words from one of the nurses or attendants relieve the anxiety in this induction stage, and the patient will usually rest comfortably in bed through this period. Following these early signs, a state of coma, or near coma, follows."

An interesting aspect of these investigations, which later in this paper will be correlated with animal experiments (Section II, E and F), concerns the attempts made to combat the central syndrome provoked by atropine. Of the many drugs considered as antidotes against atropine toxicity, eserine proved to be the most effective (52). Irrespective of the amount of atropine used to produce coma, the intramuscular injection of 4 mg of eserine within a few minutes completely restored the patient's pretreatment status. This recovery, however, was transitory, and the patient became comatose again unless further eserine was given. Similar

results with eserine were described by Wilson (183). Arecoline was ineffective in counteracting the atropine coma (52) and Ostfeld and Aruguete (126) were unable to find an antagonism of either arecoline or methacholine toward the behavioral effects of scopolamine.

d. Further effects, of a neurological character, are *the loss of coordination of voluntary movements* (*ataxia*) *and the inability to carry out complex actions* (*asynergia*). They become apparent usually after relatively high doses (10 mg and more).

e. *Hallucinations* and similar manifestations occur only after very large doses of atropine. In their studies of the psychic effects of the alkaloid, Ostfeld *et al.* (127, 128) did not encounter these phenomena with doses below 10 mg; on the other hand, Forrer (50, 51), using larger doses, did describe hallucinations, and they also appear during the course of accidental poisoning (36). Mention should be made here that pleasurable feelings have not been reported after the administration of atropine, scopolamine or related compounds (*cf.* also table 2). Furthermore, cases of addiction or abuse are seldom reported (36). Feelings of well-being have been described in postencephalitic patients given atropine; this, however, should be viewed in relation to the beneficial effect of the drug on dyskinesias. Upon cessation of the drug, no withdrawal symptoms were observed (36).

2. Scopolamine. Repeated mention is made in the literature of the more pronounced sedative properties that scopolamine has as compared with atropine (124, 127, 171). These effects appear at slightly lower doses of scopolamine (0.3 to 0.6 mg) than atropine (2 mg or more) and consist of sedation, amnesia, and drowsiness. This action, combined with its vagal blocking power, have made scopolamine a widely used preanesthetic drug. Indeed, some authors have taken rather strong positions, as for example Phelps (135), who has stated:

"There is also a sharp contrast between the sedative effect of atropine and scopolamine. Scopolamine acts as a primary depressant of the cerebrum while atropine offers little or no psychic or mental effects. Scopolamine causes definite psychic sedation in most cases and at times actual amnesia. It is this characteristic of scopolamine which resulted in its use in combination with morphine as a form of obstetrical analgesia, popularly known as "twilight sleep." Such amnesia does not follow medication with atropine alone or in combination with morphine."

On the other hand, when other reports are reviewed, one is impressed by the influence of the environmental conditions and subjective attitudes on the judgment of the responses to the drug. Scopolamine is widely used in the treatment and prevention of motion sickness; studies were therefore performed to determine the possible interference of this treatment with the ability of the men to carry out their duties. Carey and Webster (quoted in Tyler and Bard, 166) administered to 30 marines an initial dose of 0.65 mg of scopolamine, followed by 0.32 mg every 6 hours for 2 days. During this period their marksmanship was tested. Although the placebo group showed a slight superiority, "the men receiving scopolamine performed with equal efficiency before and after the administration of the drug"; the only side effect noticed was a slight drowsiness. Furthermore, De Boor (36) has reported some observations obtained from cases of self-induced or

accidental intoxication with scopolamine. Manifestations similar to those observed with atropine (*e.g.*, hallucinations, delirium, confusion) were described.

Along these lines, close examination of the data available concerning the central nervous system symptomatology produced by the two alkaloids does not permit a qualitative separation (129). It should be pointed out in particular that:

a. As a peripheral antimuscarinic agent, scopolamine is about 10 times more potent than atropine, although some exceptions have been observed. For instance, compared to atropine, scopolamine is relatively strong on the eye and on secretions, but relatively weak in its antivagal action. But it must be pointed out that a comparison of the central effects of atropine and scopolamine over a wide range of dosages has not been undertaken in man; and therefore no real substantiation of a qualitative difference on the central nervous system is yet available.

b. The frequent observation of excitatory symptoms after scopolamine administration (48, 57, 167) would indicate that the sedative effect is not the only one and that the syndrome resembles that observed after atropine. In fact, the effects of large doses of atropine (10 mg) administered to man (126, 128, 177) resemble those seen with doses of scopolamine one tenth as large. The illusions and hallucinations observed by Ostfeld *et al.* (127) after 0.8 to 4 mg of scopolamine, but not after 10 mg of atropine, appear when the dose of the latter is raised to 30 to 50 mg. (116).

c. Above a certain dosage, as in "pharmacotoxic therapy" (58) with scopolamine in place of atropine and also in accidental intoxication due to one or the other of the alkaloids (36), no differences either on the psychic or motor manifestations were noted.

3. Other anticholinergic substances. Central effects that in many ways are similar to those of atropine and scopolamine have also been described for other anticholinergic drugs. Schallek and Smith (149) have reported the side effects (drowsiness, confusion, disorientation, giddiness) of some quinuclidine esters which in the laboratory had effects like those of atropine and subsequently were submitted for clinical trial as spasmolytics. Abood *et al.* (2, 3) and Ostfeld *et al.* (125) noted psychotogenic activity in a number of piperidyl benzilates in the course of therapeutic trials to assess the antispasmodic activity of these drugs. Hallucinations, both auditory and visual, paranoid manifestations, marked alterations of the affective state, ranging from a feeling of unpleasantness to terror, were described. Although all these compounds (1) were antimuscarinic, there was little correlation between their peripheral parasympathetic-blocking and psychotogenic potencies. Abood *et al.* (3) reported the failure of neostigmine to counteract the central effects of the piperidyl benzilates in man. This result, however, cannot be used as an argument against eventual relationships between anticholinergic and psychotogenic effects because it is known that neostigmine affects mainly peripheral parasympathetic actions. Moreover, the potency of these compounds in reducing the level of cerebral acetylcholine in rats (56) and blocking the EEG effect of eserine (175) in rabbits and cats is apparently related to their reported potency as psychotomimetics.

TABLE 2

Differences in the effects of psycholomimetic drugs belonging to the anticholinergic and to the indole group

Piperidyl Benzilates	LSD, Mescaline, Psilocybine
Effects due to the block of the parasympathetic system: mydriasis, xerostomia, tachycardia, vasodilatation of skin capillaries	Effects due to stimulation of sympathetic system: mydriasis, tachycardia, hyperthermia
Slight influence on reflexes	Motor hyperreflexia
Apprehensive and anxious mood	Euphoria, pleasant feelings
Misinterpretation and isolation from the environment, tendency to introversion	Extrovertive attitude facilitating psychotherapeutic procedures
Predominantly auditory hallucinations	Predominantly visual hallucinations (kaleidoscopic)
Depersonalization only with high doses	Depersonalization commonly observed

Modified, from Cerletti *et al.* 1963 (30).

The literature also contains studies on similarities (1, 133) and differences (30) between the psychic effects provoked by these agents and those provoked by the LSD group. Pfeiffer (133) studied the central effects in man of several compounds, including atropine, scopolamine, trihexyphenidyl, caramiphen, cycrimine, prophenamine, orphenadrine, and some piperidyl benzilates, using a drug-sophisticated group who could differentiate and recognize the psychic effect of LSD. According to Pfeiffer, compounds like trihexyphenidyl, caramiphen, and JB 366 (N-methyl-3-piperidyl benzilate) produced an effect which the subjects likened to that of LSD. On the other hand, Cerletti *et al.* (30), comparing the available results, emphasized the differences between the psychosomatic symptoms produced by the anticholinergic piperidyl benzilates and those produced by LSD (table 2). In relation to the symptomatology listed in this table, it should be pointed out that many of the previously described effects of atropine and scopolamine appear to have many points in common with those provoked by the piperidyl benzilates (*cf.* also 79 and 184).

Concerning benactyzine, Larssen (86) reported in detail the symptoms observed in the course of human experimentation. These include blocking of thoughts, impairment of recent memory and of the assessment of time, heavy limb feeling, ataxia, drowsiness, dizziness and bursts of laughter. Such effects occur with 5 mg, administered either orally or subcutaneously. Hess and Jacobsen (71) reported one case in which 12 mg subcutaneously provoked restlessness, slurred speech and hallucinations. Higher doses (not specified) caused the most violent and unpleasant reactions, which can be compared to the "daymares" experienced after treatment with the piperidyl benzilates.

Bente *et al.* (11 a) reported the similarities of the central effects of two anticholinergic compounds, 1-methyl-3-pyrrolidyl-α-phenylcyclopentane-glycolate (AHR 376) and α-phenyl-α-isopropyl-glycolic acid-3-N,N-dimethylaminopropyl-ester (Bayer 1433, Wh 4849). In doses of 2 to 4 mg and 5 to 10 mg, respectively,

they produce impairment of the state of vigilance and confusion lasting several hours.

The psychic-behavioral effects of caramiphen (Parpanit) were described in the book of De Boor (36); a state of confusion and disorientation has often been reported, associated with impaired motor ability, hallucinations and alteration of proprio- and exteroception. Diethylaminoethyldiphenylacetate (Adiphenine, Trasentine) (100 to 200 mg, subcutaneously) produces similar symptoms, which Anichkov (6) described as "a sort of inebriation."

Comparing therefore the results obtained with various compounds possessing anticholinergic action, several symptoms appear to be common to the group, constituting what might be termed the "central anticholinergic syndrome," *e.g.*, impairment of thoughts, disturbances of recent memory, drowsiness, a sort of non-aggressive excitement, ataxia and asynergia, and hallucinations. Within the range of these effects, however, the different symptoms may vary in intensity, forming particular patterns for each individual drug. Scopolamine, for instance, seems to possess a higher degree of sedative power, while delirium and hallucinations are predominant in the syndrome produced by some piperidyl benzilates, such as the N-ethyl- and the N-methyl-3-piperidyl benzilate (JB 318 and JB 366).

The question arises as to whether all these manifestations can be attributed to a central cholinergic block or are dependent upon other properties of the drugs. In the following sections, dealing with other aspects of the central action of atropine and related drugs, this problem will be further analyzed and discussed.

B. Electroencephalographic effects

1. Atropine. The effects of atropine on cerebral electrical activity in man have been reported by various authors (50, 57, 60, 124, 128, 144, 177). The results are in rather good agreement. They indicate that atropine (1 to 5 mg) causes consistent shifts to low-voltage slow activity and a diminution in amplitude of the 8 to 10 cps waves which form the *alpha* activity of the EEG. This pattern is very similar to that observed in the state of drowsiness, regardless of its cause. Some workers have considered the effects of the alkaloid on the cerebral electrical activity in greater detail and have been able to make additional observations. White *et al.* (177) found that after the intramuscular administration of 1 and 9 mg of atropine there was an improvement in photic driving in 5 out of 12 subjects and a less marked blockade of the *alpha* activity on opening the eyes (Berger reaction) in 3 out of 12. According to the results of Ostfeld *et al.* (128), atropine (10 mg) reduces the EEG arousal reaction to a single flash of light.

Forrer, in 1951, (50) described the electroencephalograms (EEG) of patients who had received large doses of atropine in the course of "pharmacotoxic therapy." From his description, the tracings of these patients were not appreciably different from those described after low doses. In a recent personal correspondence on this subject, Forrer has supplied further information and samples of the EEG registered during the "atropine coma therapy." The tracing shown in figure 1 was registered during the comatose stage. Other observations on the EEG effects of high doses of atropine (25 mg and more) are those of Wilson (183) and of

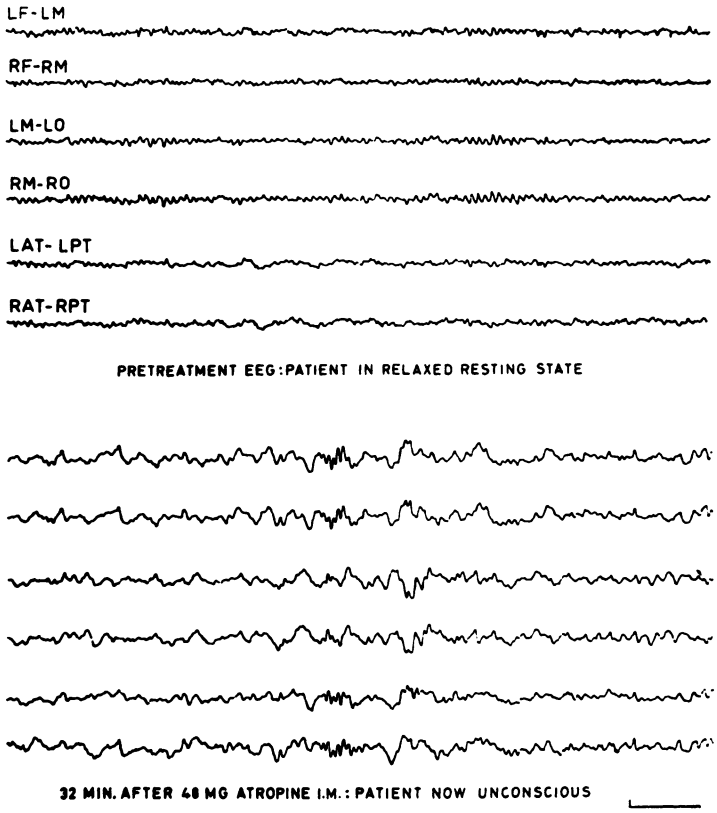

FIG. 1. Effects of high doses of atropine on the electroencephalogram of man. Upper tracing: control. Lower tracing: slow waves and spindles appear during atropine coma. Calibration: 1 sec, 50 μV. (Unpublished observation of G. R. Forrer and J. J. Miller.)

Mellerio (106). These authors, however, did not find consistent and typical EEG alterations. The patients reported by Mellerio (106) were intoxicated, and the EEG findings could be related to the antidotal treatment carried out in the hospital. In a more recent study, Wilson and Hughes (184) referred to the EEG action of atropine as "bilateral slowing of the rhythms."

With doses at which behavioral alterations can be observed, the various authors reported a fairly good relationship between them and the EEG modifications (table 3). This is especially true with respect to drug-induced drowsiness and concomitant EEG modifications. However, in some cases (124, 144) the EEG continued to have a sleep pattern at times when the patient did not exhibit sedation. Ostfeld *et al.* (128) have considered the EEG alterations in relation not only to the gross variations of motor performance but also to various "mental status examinations." Their conclusions are the following: " . . . atropine induces a shift in the human EEG rhythm towards slower activity. Evaluation of the action of atropine on behavior by means of mental status examinations, observation of spontaneous behavior and the Clyde Mood Scale have revealed alterations in

TABLE 3

Comparison of electroencephalographic and behavioral effects of atropine and scopolamine in man

Reference	Drug, Dose in mg, Route	EEG	Behavior
57	Atropine 0.6–1.3 i.v. Scopolamine 0.6–1.3	Lowering of voltages, *alpha* less evident, bursts of high-voltage waves at 10 cps	Dysartria, restlessness, clonus, then drowsiness
60	Atropine 1.2 i.v.	Decrease in voltage and frequency of the waves	No observations reported
144	Atropine 1–5 s.c.	Diminution in frequency and amplitude of the waves	At times, drowsiness was observed during the EEG modifications
50	Atropine 32 s.c.	Increase in voltage, decrease in frequency	Restlessness during first period, then sleep and coma
122	Scopolamine 1 s.c.	Thalamogram: diminution of *alpha* waves; intracortical lead: diminution of rapid activity	Drowsiness and sleep
124	Atropine 0.4–0.6 s.c, Scopolamine 0.4–0.6	Diminution of *alpha*, low voltage slow activity	Drowsiness, more evident with scopolamine
177	Atropine 1–9 i.m.	Flattening of record, decrease in frequency of *alpha*, less marked Berger reaction[a]	Loss of attention, drowsiness, ataxia
126 and 127	Atropine 10 per os, Scopolamine 0.8 s.c.	Diminution of the *alpha* index, appearance of slow waves, Berger reaction[a] to single flash blocked	Drowiness, amnesia, impaired performance of phychological tests

[a] The Berger reaction is the *alpha* blockade on opening the eyes.

the direction of reduced energy, decreased spontaneous speech and movements, impaired attention and memory and increased drowsiness. The onset, duration and termination of the behavioral effects paralleled the appearance, persistence and disappearance of slow EEG activity."

2. Scopolamine. Administered at equal or slightly lower dosages than those of atropine, scopolamine causes analogous EEG modifications (table 3). In a publication of Gibbs *et al.* in 1937 (57) a clear illustration of EEG alterations induced by scopolamine (1.3 mg intravenously) is found. These authors also mentioned the fact that atropine causes similar effects. Orkin *et al.* (124) have confirmed these observations. Okuma *et al.* (122) have reported tracings recorded from the thalamus and subcortical white matter after administration of scopolamine.

3. Other anticholinergic compounds. After giving AHR 376 (2 to 4 mg by mouth), Bente *et al.* (11a) described a diminution in the incidence and amplitude of the *alpha* waves and appearance of slow rhythms, concomitant with the mental effects. According to Wilson and Hughes (184), the clouding of the sensorium

and the hallucinations produced by Ditran[1] were often accompanied by the disappearance of the *alpha* activity.

Several investigations have been devoted to the EEG effects of benactyzine (33, 71, 136). The most conspicuous effect was the diminution in amplitude of the *alpha* activity. This change occurs simultaneously with subjective symptoms, consisting of a feeling of heaviness in the limbs and a blocking of thoughts, and is observed with subcutaneous doses of 5 to 6 mg. Hess and Jacobsen (71) gave a somewhat higher dose (12 mg) to a single subject and observed, in addition to the disappearance of the *alpha* waves, a later occurrence of slow activity; restlessness, confusion, slurred speech and hallucinations were also present. The performance of the subjects on a reaction-time test was also tested (72); disappearance of the *alpha* activity and increase of both latency of response and number of errors were parallel. The similarity of these results with those of Ostfeld *et al.* (128) and of Ostfeld and Aruguete (126) with atropine and scopolamine, is evident. Also the finding of an amelioration of the photic response (71) fits with the results obtained by White *et al.* (177) with atropine.

In summary, diminution in amplitude of the *alpha* waves and occurrence of slow activity seem to be the characteristic signs of the central effects of the anticholinergic drugs. Other phenomena described, although not appearing consistently, were blocking of the "Berger reaction" and improvement of photic driving.

4. Effects of atropine and scopolamine on abnormal electroencephalographic patterns. Atropine and scopolamine modify the EEG patterns in various pathological states. The use of these compounds in cranio-cerebral injuries was prompted by laboratory results that indicated a high content of acetylcholine in the cerebrospinal fluid during cerebral trauma or after electroshock therapy (16, 172). In patients suffering from concussion, after treatment with scopolamine there is a shift towards normal in the altered EEG (87). Ulett and Johnson (167) reported that the high-voltage *delta* activity observed in the process of electroconvulsive therapy was blocked by the administration of atropine and scopolamine. Fink (48), however, found other anticholinergic compounds (diethazine, benactyzine, N-ethyl-3-piperidylbenzilate or JB 318, and 2-diethylaminoethyl-cyclopentyl-2-thienyl-glycolate or Win 2299) more active and envisaged a broader use of such drugs with less effect on the peripheral nervous system and more effect on the cerebrum.

On the EEG expressions of epilepsy, atropine seems to have different effects depending upon the type of seizure. In *grand mal* a reduction of the anomalies observed in the interictal periods is achieved (60). In patients with temporal lobe epilepsy, atropine activates the temporal foci (117). Forrer (personal communication) has confirmed the activation of local discharges.

II. EFFECTS IN ANIMALS

A. Behavioral studies

The syndrome of mixed excitation and depression caused by atropine and scopolamine in man is also found in animals, along with the large differences be-

[1] Ditran or JB 329 is a mixture of two compounds: 1-ethyl-3-piperidyl-phenylcyclopentyl-glycolate and 1-ethyl-2-pyrrolidyl-methyl-phenylcyclopentylglycolate.

tween the dose producing effects and the lethal dose. Unfortunately, gross observation of the effects gives little or no indication of the type of central action of this drug. Upon consultation of the literature one is impressed by the number of different interpretations applied to the results obtained. Bijlsma and Brouwer (14), who have described in detail the syndrome caused in the dog by scopolamine (5 to 50 mg, subcutaneously), emphasized the similarity of the behavior of treated animals with that of animals after decortication. Barlow (9) analyzed the central effects of scopolamine in the rat, in relation to its role in morphine-scopolamine "twilight sleep." He described the sedative effects obtained with small doses of the alkaloid (0.1 to 10 mg/kg). He could find no potentiating effect of scopolamine on nitrous oxide anesthesia. Also, the addition of scopolamine to morphine in preanesthetic medication for nitrous oxide anesthesia had no synergistic or additive effects. Therefore, the author advanced the hypothesis that scopolamine action in man is not so much a narcotic effect, but rather it produces a state of disorientation and amnesia. Yet scopolamine and atropine potentiate the action of barbiturates in rats (56). Meyers and Abreu (111) performed a comparative study of the central and peripheral effect of a series of anticholinergic drugs. They reported a mixed syndrome of excitability and depression in the dog with both atropine and scopolamine (1.5 mg/kg). They likened this syndrome to the delirious state that occurs during the second stage of anesthesia. White *et al.* (176) reported a phylogenetic comparison of the central actions of atropine and scopolamine. In a number of animal species (rabbit, dog, monkey) they found only quantitative differences between atropine and scopolamine. In the dog, for example, at doses from 1.5 to 50 mg/kg of atropine or from 1.5 to 150 mg/kg of scopolamine, there was little difference between the syndromes. According to the authors' description, which recalls in many ways that of Bijlsma and Brouwer (14): "Hyoscine given s.c. or i.m. in 1.5 mg/kg doses to 8 dogs, produced behavioral effects similar to that seen in 9 dogs receiving 100 to 150 mg/kg. Likewise, atropine in 1.5 and 50 mg/kg doses by the same routes induced in 7 and 8 animals respectively behavioral changes indistinguishable from that obtained with hyoscine. Within 2 to 10 minutes all of these animals manifested a slow, often stinted gait, which might be termed ataxia. At this time, most retained responsiveness to the calls and handling of the investigators. . . . Within 15 to 20 minutes after the injections, however, they wandered slowly and aimlessly and lost interest in their surroundings. Most of these animals (73%) displayed a forward compulsive gait, walked into objects or attempted to 'push through' such objects. Sixty-five per cent whimpered, barked or yelped aimlessly sometime during this period. They appeared confused or 'lost' which might appropriately be called 'delirium'. None of these animals ran or jumped. . . . Sleep, usually deep, followed this delirious period. . . . The onset of sleep was not related to dose. Loud noises or nociceptive stimuli would usually cause the sleeping animals to open their eyes and raise their heads slightly. Occasionally, running movements and whimpering accompanied the sleep. In most cases the sleep period lasted 8–25 minutes and was thereafter intermittent. . . . Most of the animals recovered from the marked effects in 5–7 hours and, except for mydriasis, were apparently normal in the next day." In monkeys also,

the effects were independent of the dose, and under the drug these animals appeared intermittently in coma, sleep, or wakefulness. The rabbit showed very slight variations of overt behavior; after decortication, however, a relaxing effect of atropine on the striated muscular system was noticed. This had already been observed by Mehes (105) with scopolamine, and he attributed this muscle-relaxing action to a hypnotic effect. White *et al.* (176) concluded that these drugs possess a high specificity in that, once the peripheral and central cholinergic receptors are saturated, they do not cause other types of toxic action.

The findings resulting from these behavioral studies raise the question whether the gross effects observed in animals can be considered an adequate index for analyzing the action of these drugs on behavior. Far too often, the indications that these changes take place at a higher cerebral level are insufficient and, equally often, the attempted interpretations are misleading. A better evaluation of the behavioral changes due to the anticholinergic drugs is offered by the results obtained when more discriminating techniques are used. These involve, first, the effects of the drugs on some forms of motor pattern provoked by other drugs or by lesions in the brain and on motor responses of a less integrated nature (*e.g.*, in attempts to localize the action of the drugs) and second, results obtained through a careful observation of the innate response of the animals to environment.

1. Effects on evoked motor patterns. Juul (82) first reported that atropine and scopolamine reduced the tail erection (Straub-Herrmann reaction) provoked by morphine in mice. The minimal effective dose indicated by Juul is 0.5 mg/kg for scopolamine and 50 mg/kg for atropine, whereas Holten later found (76) the two drugs equally effective at 10 mg/kg and Parkes (129) gave figures of 1 to 2 mg/kg for scopolamine and 20 mg/kg for atropine, thus confirming the ratio common to other central actions of the two drugs.

Some of these experiments were performed in order to study the central effects of atropine and scopolamine in relation to their therapeutic effects in Parkinson's disease. Even though the effectiveness of the belladonna alkaloids in this disease has been known since the times of Charcot, research in this field is relatively recent and arose from the clinical use of new antiparkinsonian drugs. Investigations have been performed to examine the sites of action of these drugs and to develop laboratory methods for the screening and assaying of substances potentially effective in disorders in which rigidity and tremors are characteristic. Scopolamine and atropine both possess a marked antitremor effect in the monkey. This is true regardless of whether the tremors are caused by electrical stimulation of the reticular formation in anesthetized animals (81) or are present in monkeys with lesions in the midbrain reticular formation and in the posterior subthalamus (168). In both cases scopolamine was 10 times more potent than atropine. Both alkaloids also antagonized tremor, spasticity, and other effects provoked by tremorine (1,4-dipyrrolidine-2-butyne) (46) or arecoline (6). In cats, tremorine causes a marked rage response, which can be prevented by atropine (8) or by a number of other drugs having atropine-like action (164). Atropine, scopolamine and other anticholinergic drugs such as methyl-benactyzine and caramiphen antagonize the increase of blinking provoked by arecoline in pigeons (84) and

have a releasing action on the catatonic syndrome provoked in rats by some phenothiazine derivatives (120). Also the "circling behavior" or the torsion of the head provoked by the intracarotid administration of anticholinesterases (DFP, eserine) is eliminated by anticholinergic drugs. In monkeys and in guinea pigs scopolamine abolishes this motor pattern sooner and in smaller doses (0.1 to 0.4 mg/kg) than atropine (1.2 to 1.5 mg/kg) (37, 44). Mention should be made that other drugs with antiparkinsonian properties (caramiphen, diethazine, trihexyphenidyl) counteract tremor in the monkey, the syndrome provoked by tremorine, and "circling behavior." Interestingly enough, these drugs also show an antagonistic effect towards nicotine-induced convulsions, which are not affected by atropine or scopolamine (96).

The school of pharmacology of Utrecht has undertaken several investigations on the locus and mechanism of action of anticholinergic drugs. Teuchmann (163) and later De Maar (38) observed that atropine and scopolamine decreased the ipsilateral flexor reflex of the thalamic cat, while they were ineffective in the decerebrated or decapitated preparation. Proceeding from previous investigations of Bijlsma and Brouwer (14) on the behavioral effects of scopolamine, Bijlsma and Funcke (quoted in 13) showed that in the decorticated cat a dose of 1 to 2 mg/kg of this drug provokes ataxia of a much more marked character than that observed in intact animals.

All the above data suggest that atropine and scopolamine, together with other anticholinergic drugs, are able to control various types of drug-induced motor pattern and to restore a balance when certain neurological deficits are created. However, there is still the problem of identifying the cerebral systems involved. In this connection, it is interesting to note that all the authors referred to advanced the hypothesis of a more or less direct action on specific cerebral areas. Essig *et al.* (44) associated the circling movements mainly with the variations of acetylcholine content in the caudate nucleus. De Jonge and Funcke (37) attributed the torsion syndrome to an asymmetrical acetylcholine distribution in the brain stem, caused by localized cholinesterase inhibition at the level of the vestibular nuclei. Jenkner and Ward (81) suggested that partial deafferentation of certain brain stem areas provokes a local hypersensitivity to endogenous acetylcholine, and that this alteration plays a causative role in Parkinson's syndrome. The experiments of the Utrecht school have shown, however, that hypersensitivity caused by denervation is not necessarily involved. An acute ablation of the rostral areas of the cerebrum is sufficient to alter the balance of central regulation of basic spinal reflexes. According to Bijlsma (13): "la scopolamine excerce une influence sur les noyaux diencéphaliques ou mésencéphaliques, si ceux-ci sont libérés de leurs connections avec le télencéphale." In particular, the results of De Maar (38) point to the ventrocaudal part of the diencephalon, which includes the *substantia nigra*, as the site of action of the drugs.

Other results indicate the existence of an effect at more rostral levels. Upon local application to the cortex of acetylcholine or acetylcholine and eserine, localized or generalized convulsions ensue. The convulsions can be prevented or terminated by atropine, by either local or systemic administration (7, 115). The

hypothesis of the existence of a cholinergic system even at the cortical level is confirmed by the high specificity of the atropine effect, which exerts its antagonistic action only in relation to the alterations caused by cholinergic drugs (*cf.* also the section on the EEG effects). In this connection, we have also to consider the possibility of different sensitivities of the central cholinoreactive structures to atropine, analogous to those of "muscarinic" or "nicotinic" receptors in the periphery (134). Anichkov (6), in setting forth this concept, drew attention to a series of investigations of Russian pharmacologists, showing a differential effect of anticholinergic drugs in antagonizing the central action of nicotine or arecoline.

2. Effects on unlearned behavior. The recording and measurement of locomotor activity has been widely employed for assessing the central effects of drugs. In the literature, data are found indicating that atropine (10 to 20 mg/kg) and scopolamine (0.2 to 1 mg/kg) cause an increase of bodily activity in rats (120, 169) and mice (68).

The influence of atropine and of scopolamine on the orientational hypermotility of mice has been studied by Parkes and Lessin (130). The orientational reflex is a form of unlearned reactivity, manifest in animals transferred from their customary environment to a new one. Whereas mice placed in a cage show an exploratory behavior that declines in a short time, treatment with atropine and scopolamine prolongs this locomotor activity. This effect and the suppression by scopolamine of spontaneous alternation in rats , described by Parkes (129) and by Meyers and Domino (109), could be explained, as these authors suggest, by the interference of this drug with the organization of sensory information that regulates the reaction of the animals. Perhaps this can account also for the inhibition of isolation-induced fighting in mice by scopolamine (80). An increase of both exploratory activity in an open field and spontaneous lever-pressing were observed by Tapp (162) after atropine in the rat. In all these experiments, scopolamine was effective in minute amounts (from 0.06 to 0.3 mg/kg), the ratio between scopolamine and atropine varying from 30:1 (129, 130) to 50:1 (80).

B. Effects of atropine and scopolamine on acquisition and retention of conditioned responses

For the study of the effects of psychotropic drugs on behavior, the methods of experimental psychology have been fully adopted by pharmacologists. Undoubtedly, investigations of centrally acting substances have led to deeper insights because of the introduction of these techniques for evaluating animal behavior. In the case of the anticholinergic drugs, we have an example of how such techniques can provide information on the alterations of central homeostasis responsible for the changes in behavior.

In arranging the relevant material, several difficulties have arisen in the interpretation of the results when the two viewpoints of pharmacologists and psychologists are considered on some particular problems. Therefore it was felt to be more appropriate to present the data in table form (tables 4 and 5) with relevant comments in the text. The doses listed in these tables refer to the lowest dose that caused the changes indicated under the column "effect."

TABLE 4a

Effects of atropine and scopolamine on discrete trial avoidance

Species and Technique	Atropine	Scopolamine	Effect	References
	mg/kg	*mg/kg*		
Rat—pole jumping	5		0	134
Rat—pole jumping	32[a]		−	43
Rat—pole climbing	100		0	
Rat—pole climbing		10	+	66, 67
Rat—pole climbing (recently acquired)		1	−	
Rat—pole jumping	15		−	170
Rat—pole jumping	8[a]	1	0	110
Rat—pole jumping	5		−	154
Rat—jumping box		30	0	121
Rat—jumping box	15		0	19
Rat—two-compartment cage	0.5	0.01	+	77
Rat—shuttle box	10		0	26
Rat—shuttle box	32		0	95
Rat—shuttle box	50	0.5	+	12
Mouse—runway (?)	5		0	101
Cat—barrier crossing or limb withdrawal	1.2		0	53
Monkey—limb withdrawal	1		−	137
Rat—passive avoidance (one learning trial)	6		−	24
Rat—passive avoidance (overlearned)	6		0	
Rat—passive avoidance		0.2	−	108

Indication of effect is given as follows: 0 = no change; − = worsening of the performance; + = improvement of the performance.

[a] = *l*-Hyoscyamine

[b] = With warning stimulus

[c] = Simultaneous

[d] = Successive "go-no go"

[e] = Study of generalization gradients

We will first consider the effects on previously acquired conditioned behavior. The material has been classified into two sections, dealing with avoidance and with reward conditioning. Table 4 summarizes the results obtained by the use of avoidance techniques. These have been divided into discrete trial avoidance, continuous (Sidman type) avoidance, and miscellaneous avoidance techniques involving some kind of discrimination.

Discrete trial avoidance (table 4*a*) is seldom affected by atropine or scopolamine; in some cases improved performance has been described (12, 67, 77). Adverse effects can sometimes be observed when the conditioned response has been acquired recently (24, 66) or with techniques involving more complex motor performance (43, 154, 170). In the evaluation of these results it should be kept in mind that most of the data refer to the rat. When a higher animal was used, as in the experiments performed in monkeys (137), a block of the response was found with doses of atropine as low as 1 mg/kg.

In experiments involving discrimination (table 4*b*), adverse effects were not observed more frequently than with simple avoidance. In the rat an increase of responses to the negative stimulus was described (18). Also the analysis of generalization gradients in the monkey showed an increase of operant lever-pressing proportionally greater during the presentation of negative stimuli, as compared with positive stimuli (64).

TABLE 4b

Effects of atropine and scopolamine on avoidance with discrimination

Symbols as in table 4a.

Species and Technique	Atropine	Scopolamine	Effect	References
	mg/kg	*mg/kg*		
Rat[c]—3-compartment box		10	0	121
Monkey—"visual discrimination test"	1	0.03	—	107
Rat[d]—pole climbing (recently acquired)		1	–	66,67
Rat[d]—pole climbing (overlearned)		1	0	
Rat[d]—jumping box	15		0	19
Rat[d]—shuttle box	32		0	95
Rat[d]—shuttle box	50	0.5	–	18
Monkey[e]—continuous (Sidman type)		0.05	–	64
Rat—multiple U maze (recently acquired)		0.5	–	132
Rat—multiple U maze (overlearned)		10	–	

TABLE 4c

Effect of atropine and scopolamine on continuous avoidance (operant lever-pressing, Sidman type)

Species	Atropine	Scopolamine	Effect		References
			Response rate	Shocks avoided	
	mg/kg	*mg/kg*			
Rat		0.1	+	0	65
		1	−	−	
Rat	20		0	−	28
Rat	8	4	+	0	157, 158
Rat		0.2	+	?	120
Monkey		0.2	0	0	22
Rat[b]		2	+	0	55

Symbols as in table 4a.

Continuous avoidance (Sidman type) experiments have been considered separately (table 4c) since, in addition to the drug effect on the number of shocks avoided, they give an indication of absolute changes in response rates independently of the presentation of any external conditioning stimulus. At the doses tested, the efficiency of avoidance responding is sometimes lowered by the drugs, but more frequently is unchanged. In most cases the drugs augmented response rates. This has been attributed to the increase of general activity, to disruption of timing behavior, or to changes in aversion level. Whichever is the cause of this increase, it should be noted that the increase appears with very low doses of scopolamine (0.05 mg/kg for the rat and 0.01 mg/kg for the monkey). The data of Stone (157), which concern also the effects of atropine and benactyzine, emphasize discrepancies between individuals of the same strain in the response to a drug, rather than differences among drugs.

In table 5 are presented the results obtained with conditioned behavior based on reward. Atropine and scopolamine proved to be very effective in disrupting instrumental and operant reward conditioning and maze performance.

Some doubts have arisen as to whether the disruptive action of atropine on food reward tests is due to a central anorexic action or to its peripheral effects (dry mouth, reduced gastric secretion), which might reduce the animal's desire to eat and in turn worsen its performance. An anorexic effect has, in fact, been demonstrated concomitant with the inhibited conditioned performance (26). Stein (155) and Whitehouse *et al.* (181) showed that the anorexic effects were more likely to be peripheral. They showed that in rats atropine and methylatropine were equally effective in diminishing food intake. Only atropine, however, disrupted the search for food in the maze exercise (181). It must also be

TABLE 5

Effects of atropine and scopolamine on reward conditioning

Symbols as in table 4a.

Animal Species and Technique	Atropine	Scopolamine	Effect	References
	mg/kg	*mg/kg*		
Instrumental				
Dog—food motor reflex	0.17		–	142
Rabbit—ring pulling		0.1	–	145
Rat—lever pressing with successive conditional discrimination		0.2	–	63
Rat—successive "go-no go" discrimination	5		–	170
Rabbit—ring pulling with successive "go-no go" discrimination	0.5	0.05	–	95, 104
Rat—successive conditional discrimination	2			181
Operant				
Rat—lever pressing (fixed ratio)	4	0.1	–	17
Monkey—lever pressing (fixed ratio)		0.2	–	22
Rat—lever pressing (continuous reinforcement)	10		–	26
Rat—lever pressing (alternation)	2	0.1	–	27, 29
Rat—lever pressing (alternation)		0.2	–	63
Rat—multiple choice discrimination	6	0.1	–	27, 29
Rat—lever pressing (fixed ratio)	4		–	168a
Mazes				
Rat	2	0.1	–	102
Rat	2		–	88
Rat	15	1.7	–	42
Rat	25		–	19

observed that in the work of Sadowski and Longo (145) explicit note was made of the fact that after doses of scopolamine that blocked instrumental reward conditioning, the animals accepted food that was presented directly to them. Furthermore, very small doses of anticholinergic drugs blocked operant reward conditioning involving some kind of temporal discrimination, *i.e.*, differential reinforcement of low rates of lever pressing (27, 29) or fixed-interval schedules (17, 65). The increase in response rates described in these experiments does not support the hypothesis of a reduction in motivation level.

Since the tables refer only to experiments carried out in mammals, the results obtained in pigeons will be mentioned separately. Scopolamine (0.01 to 0.1 mg per bird) depresses the absolute rate of key-pecking in a variable-interval schedule. Contrary to what is observed in the rat, the performance in a successive "go-no go" discrimination is unaffected (39, 40).

The effects of atropine and other anticholinergic compounds have also been studied on two other aspects of conditioned behavior: acquisition and extinction. The results obtained reveal a striking action of these compounds, an interference with the learning process and with the extinction phase. Particularly interesting results have been reported by Herz (67), who studied the effects of anticholinergic drugs on the complete cycle of conditioning and extinction in the rat. This author used the "pole-climbing" technique and was able to demonstrate that atropine and scopolamine, when administered during the period of formation of the avoidance reflex, caused notable alterations in the response, while they were inactive in fully trained animals. These observations on the deleterious effect of atropine on the learning process have been confirmed by Meyers *et al.* (110), using the same technique, and by Whitehouse (180), who found that atropine was able to hinder the learning of a successive conditional discrimination. Also the learning of passive avoidance is hindered by atropine or scopolamine (24, 41, 108). Lukomskaja (101) found that atropine interferes with the acquisition of a conditioned avoidance reflex in mice, and Ricci and Zamparo (137) described the same effect in the monkey.

Both atropine and scopolamine also cause a "freezing" of previously learned tasks, so that they become particularly resistant to the normal extinction processes. The lengthening of the extinction period has been verified in experiments involving both avoidance (24, 28, 29, 65, 67) and reward (26, 63, 64, 112).

From the results obtained with conditioning techniques, the following effects can be listed as characteristic of the anticholinergic drugs: 1) little influence on discrete trial avoidance, 2) disruption of instrumental and operant reward conditioning and maze performance, 3) adverse effects on learning, and 4) lengthening of the extinction period of previously learned tasks.

An interpretation of the mode of action of anticholinergic compounds on learned behavior has been advanced by Carlton (28), who stated: "The attenuation of the cholinergic function is correlated with the attenuation of the normal consequences of non-reinforcement." In fact, in a variety of situations [extinction (24, 26, 28, 29, 63, 65, 112), fixed interval schedules (17, 65), alternation (27, 29,

109, 129), various kinds of discrimination (18, 27, 29, 63, 121, 170), and "generalization gradient" tests (64)] anticholinergic agents cause reappearance of previously suppressed responses, perseveration of response, or both. However, according to the hypothesis of Carlton, anticholinergic agents should cause these effects only when disinhibition or perseveration of response does not involve punishment or loss of reward (*e.g.*, in fixed interval schedules, extinction situations). It should be pointed out (*cf.* also 156) that similar results have been observed when the experimental situation involves loss of reward (differential reinforcement of low rates of lever pressing, 27, 29) or punishment (successive "go–no go" discrimination with punishment of responses to the negative stimulus, 18). In view of this evidence, the effect of the anticholinergics cannot be limited to an "attenuation of the normal consequences of non-reinforcement" but must involve a broader influence on the mechanisms regulating control of motor response.

C. Effects of atropine and scopolamine on the electrical activity of the brain

There is a vast literature concerning the effects of atropine and related compounds on the EEG of laboratory animals: monkey (43, 176), dog (43, 149, 176, 182), cat (20, 23, 47, 54, 62, 90, 131, 148, 165, 173), rabbit (35, 61, 68, 92, 93, 138, 174), and rat (15, 110, 147). Within a short time (1 to 2 minutes) after the injection, in all species the modifications of the tracing follow a common pattern. Bursts of 8 to 12 cps waves, similar in many aspects to "spindles," intermingled with high-voltage slow (2 to 5 cps) waves, appear in the anterior leads. Slow activity is seen also in the posterior and subcortical leads. These changes are very similar to those occurring during rest or sleep and are broadly classified as EEG synchronization. For atropine the synchronizing doses range, in the various species and preparations used, from 0.2 mg/kg in the "encéphale isolé" cat to 6 mg/kg in the rat. In addition to the changes of the spontaneous EEG, other modifications have been described. After administration of doses slightly higher than those required for synchronization, physiological sensory stimuli no longer have any "activating" or "desynchronizing" effect on the cortical electrical rhythms. At the hippocampal level the 4 to 6 cps activity characteristic of the activated tracing is replaced by irregular slow waves with superimposed 20 to 30 cps low-voltage activity. The threshold of activation upon electrical stimulation of the reticular substance or of the non-specific thalamic nuclei is significantly raised. Detailed analyses of this phenomenon can be found in the literature. Bradley and Key (21) studied in the *encéphale isolé* cat the effect of graded doses of atropine on the threshold of EEG arousal produced by electrical stimulation of the reticular formation. Doses higher than 0.2 mg/kg caused the threshold to rise progressively; the maximum effect was observed with 2 to 4 mg/kg, which raised the voltage up to 4 times the original values. Similar results have been obtained by other investigators using both curarized (103) and *encéphale isolé* preparations of cats (90, 148, 165) and curarized or non-curarized unanesthetized rabbits (92, 139).

In these various experiments there is general agreement that, above a certain

TABLE 6

Comparison of the minimal doses of atropine and scopolamine that synchronize the EEG

	Atropine	Scopolamine	References
	mg/kg	*mg/kg*	
Rat	8 s.c.[a]	1 s.c.	111
Rabbit	0.5 i.v.	0.04 i.v.	92
	2 i.v.	0.1 i.v.	174
Cat	0.4 i.v.	0.1 i.v.	47
	0.3 i.v.[b]	0.05 i.v.	21
	1 i.v.	0.1 i.v.	148

[a] = *l*-hyoscyamine.
[b] = encéphale isolé.

dose, no additional important modifications in the tracing are encountered. In the cat Wescoe *et al.* (173) reported the same changes after doses varying from 1 to 40 mg/kg, and Paul-David *et al.* (131) found the same result with 0.2 to 10 mg/kg. In the rabbit, Rinaldi and Himwich (138) administered doses of 0.5 to 30 mg/kg and Longo (92) doses of 0.5 to 10, without finding additional alterations of the tracing. White *et al.* (176) made the same observation for doses varying from 1.5 to 50 mg/kg in the dog. Only one case of a *grand mal* EEG pattern has been described, occurring after administration of 700 mg/kg subcutaneously in the rat (147). In rabbits, a desynchronizing action of atropine at extremely low doses (5 to 20 μg/kg, intravenously) was reported (10, 61). According to Schallek and Smith (149), atropine increased the frequency of the EEG in curarized dogs at 0.1 mg/kg intravenously, whereas after 1 mg/kg slow activity appeared. In our laboratory, experiments performed with the method of "remote injection" both in acute preparations and in rabbits with chronically implanted electrodes, failed to confirm this diphasic effect of atropine (95).

The alterations produced in the EEG by scopolamine are analogous to those of atropine, but lower doses are required. Table 6 lists results obtained during parallel studies. These data show that scopolamine is from 4 to 20 times more potent in eliciting the synchronization of the EEG. In the dog and in the monkey doses of 1.5 mg/kg of either atropine or scopolamine synchronize the EEG, but the comparison of minimal doses has apparently not been made.

In analyzing these effects, it is still not clear to what extent the peripheral effects of these drugs influence the EEG patterns. Quaternary derivatives have a peripheral anticholinergic potency equal to, or superior to, those of atropine and scopolamine but do not easily penetrate to the cerebrum. These compounds have been used in comparative studies and had little or no effect on the EEG. Negative results have been reported in the cat after administration of dibutoline 10 mg/kg (54) or methantheline (Banthine) 10 mg/kg (47). With methylatropine, however, Domino and Hudson (43) observed a synchronization of the rat's EEG after administration of 16 mg/kg, Paul-David *et al.* (131) showed a late syn-

chronization in the *encéphale isolé* cat after intravenous administration of 1 to 2 mg/kg, and in the curarized cat Szerb (160) reported a synchronization after 4 mg/kg. Investigations carried out in our laboratory on rabbits with chronically implanted electrodes did not show immediate or late alterations of the tracing after intravenous doses of methylatropine up to 5 mg/kg (95). The relative central activity of several anticholinergic drugs with tertiary and quaternary ammonium structures was investigated by Herz *et al.* (70). The minimal doses to produce central and peripheral actions were measured by various methods. The results showed that the central activity is related to the lipid solubility of the drug. If a drug with poor lipid solubility is allowed to permeate long enough from the blood to the brain, it finally reaches an equilibrium distribution. This may explain the synchronization observed after methylatropine by some investigators (43, 131, 160).

Electrophysiological investigations have also dealt with other aspects of the influence of these drugs on brain electrical activity. Neither atropine nor scopolamine influences significantly the reticular potentials evoked by single shocks applied to peripheral nerves (98, 178). As pointed out by Longo and Silvestrini, this fact differentiates the anticholinergics from the barbiturates, which, besides provoking a synchronization of the EEG, markedly depress evoked responses. A notable enhancement of peripherally evoked cortical responses on topical application of 2 per cent atropine was described by Chatfield and Purpura (32) and by Chatfield and Lord (31). These authors postulated the existence of a cortical inhibitory mechanism which is blocked by atropine. Szerb (161) confirmed their observation and also described a diminution of the secondary complex of the response. In direct relationship to the problem of central cholinergic transmission, this author measured the cortical acetylcholine output and found a notable increase during the EEG activation due to stimulation of the reticular formation. Atropine blocked the EEG activation without affecting the increase in acetylcholine output (83). Mitchell (118) showed, however, that atropine alone increases the output of acetylcholine in the cortex, and other authors (56) found a diminution of acetylcholine content in the rat brain after scopolamine or atropine.

From the studies of the effects of these drugs on cerebral electrical activity, the following conclusions can be drawn. There seems to be no qualitative difference between the EEG effects of atropine and scopolamine, but the latter has the same effects at lower doses. The modifications of the tracing can be attributed mainly to a direct action on the brain cells. The present status of our knowledge does not allow identification of the system (or systems) responsible for these modifications, although several hypotheses have been advanced in relation to the electrophysiological analysis of the action of atropine on the central nervous system. The writer has gathered from the literature three different interpretations on its site of action, based on similarities with the symptomatology obtained after ablation or destruction of some central areas. On the basis of the mere observation of gross behavior, the effect of atropine has been compared to decortication (14, 176). When techniques based on learned behavior are involved, the

modifications produced by the drug show some similarities to those observed after hippocampal ablation (110). In the light of electrophysiological studies, the EEG produced by atropine was compared to the pattern of changes obtained after bilateral lesions of the posterior hypothalamic-thalamic complex (165).

Perhaps, the discrepancies among these data will become clarified once the notion is accepted that discrete and mutually interacting brain systems are cholinergic in nature and all involved in the central effect of the drug. In this connection there is some evidence for a dichotomy in the central cholinoreceptive structures, similar to the peripheral subdivision into muscarinic and nicotinic classes. On the basis of the present results, it seems that atropine and scopolamine possess a high and specific affinity for the muscarinic system.

D. Effects of other anticholinergic compounds on cerebral electrical activity

The administration of benactyzine induces EEG changes which strongly resemble those of atropine and scopolamine. In curarized cats (11), the fast activity of the electrocorticogram is greatly reduced and irregular outbursts of 8 to 15 cps waves appear both in the cortical and subcortical leads; these changes appear after intravenous administration of 0.5 or more mg/kg. A somewhat lower dose (0.1 mg/kg) was found effective by O'Neill and Vernier (125), using the same preparation; EEG arousal responses following tone or pinch were attenuated at doses of 0.2 and abolished at 0.6 to 1.8 mg/kg. A partial block of the EEG activation upon electrical stimulation of the reticular formation in the *encéphale isolé* cat was obtained by Schallek and Kuehn (148) after 1 mg/kg. Essentially similar results were described in the rabbit (75, 153). As is the case with atropine, increasing the dose up to 100 times that minimally effective on the EEG (from 0.05 to 5 mg/kg) did not provoke further changes in the EEG picture (153). In the rabbit, White and Carlton (175) studied the EEG effects of four piperidyl benzilates and reported a good correlation between the atropine-like effects on the EEG (synchronization, block of the effects of exteroceptive stimuli) and the reported psychogenicity of the same agents in man. In particular, Ditran (JB 329) was able to cause EEG synchronization in the rabbit at intravenous doses as low as 0.005 mg/kg; thus it is the most potent of the anticholinergic compounds in affecting the electrical activity of the brain. Analogous effects of Ditran, although at higher doses, have been reported in the cat (78, 143, 175).

EEG studies have shown that many of the drugs used in the therapy of parkinsonism (diethazine, ethopropazine, caramiphen, trihexyphenidyl) lead to changes similar to those due to atropine (69, 100, 140). According to Himwich and Rinaldi (74) the effectiveness of drugs in the treatment of Parkinson's syndrome is directly proportional to the degree to which their EEG effects mimic the action of atropine. Furthermore, others reported that anti-Parkinson agents are more effective in blocking the EEG effects of eserine than are chemically related compounds that do not affect parkinsonism (179). One should note, however, that all these drugs produce synchronization at relatively high doses, and do not show the high specificity of EEG effects characteristic of atropine and scopolamine. In this connection, White and Boyajy (174), in a comparison of the EEG alterations induced

TABLE 7

EEG and behavioral effects in rabbits of high doses of anticholinergic compounds

Drug	Dose	Occurrence of Diphasic EEG[a]	Behavioral Excitement	EEG and Behavioral Seizures
	mg/kg i.v.			
Atropine	45–60	0/11	0/11	0/11
Scopolamine	45–60	0/8	0/8	0/8
Benactyzine	4–15	0/5	5/5	3/5
Diphenhydramine[b]	8–15	2/14	14/14	5/14
Hydroxyzine[c]	10–20	5/16	16/16	7/16

From White and Boyajy 1960 (174).

[a] = A diphasic EEG is one characterized by alternation of synchronized and desynchronized tracings.

[b] = Analogous results obtained by Rinaldi and Himwich, 1955 (138), who described an EEG alert pattern after 10–20 mg/kg of diphenhydramine and trihexyphenidyl.

[c] = The results of Silvestrini, 1958 (153), agree with the less pronounced synchronizing action of hydroxyzine.

by several anticholinergic compounds, were able to demonstrate the occurrence of both EEG and behavioral seizures after high doses of benactyzine. These collateral effects were even more evident with other diphenylmethane derivatives. Therefore, these drugs must be considered as having, in addition to their central anticholinergic action, other effects. In table 7 are summarized the results of White and Boyajy, supplemented by findings of other investigators along the same lines. It should be mentioned also that all the anti-Parkinson drugs, in contradistinction to atropine and scopolamine, are able to counteract the EEG picture of *grand mal* provoked by nicotine (100). It seems, therefore, that the anticholinergic effect of these compounds is due to both antimuscarinic and antinicotinic properties.

E. Antagonistic effects of anticholinergic and cholinergic compounds on cerebral electrical activity

The striking effect of anticholinergic drugs on various aspects of cerebral electrical activity lends further support to the theory that acetylcholine plays a role in transmission within the central nervous system and, more specifically, in cerebral electrogenesis. There have been several investigations of the antagonism of anticholinergic drugs to the changes in cerebral electrical activity induced by acetylcholine and cholinesterase inhibitors. Atropine abolishes acetylcholine-induced activation of the EEG (91, 138); it also counteracts the activations induced by arecoline, tremorine, and pilocarpine, injected intravenously (45, 69, 119). The EEG picture of synchronization caused by atropine or scopolamine is cancelled by the administration of eserine and, conversely, eserine-induced desynchronization is antagonized by atropine. Within certain dose limits it is possible to obtain a prevailing picture of synchronization or desynchronization according to the drug ratio used (99). Many authors have pointed out that these drastic changes of cerebral electrical activity are not accompanied by modifications of the overt behavior of the animal; these results have been interpreted

within the framework of a theory of "dissociation" between the EEG and behavioral effects (78) (see Section II F).

The antagonistic features also extend to the electrical *grand mal* picture often observed after administration of high doses of some cholinesterase inhibitors such as DFP (44, 173), TEPP (159), and sarin (97). When DFP is injected in large dose (either intravenous or intracarotid), an EEG picture of *grand mal* ensues, accompanied by more or less generalized motor convulsions; atropine, administered intravenously (1 to 2 mg/kg) terminates or prevents both the EEG and the motor phenomena (44, 61, 73). Other antagonistic phenomena in which motor and electrical signs run parallel are those described by Miller *et al.* (115) in cats and rabbits: after application of acetylcholine to the previously eserinized cortex, spikes appear in the electrical record, accompanied by motor effects consisting of movements of the vibrissae, tremors, and mastication. Atropine administered either systemically (1 mg/kg) or locally (0.2 per cent) prevents the induction of the spikes and the motor effects. These results have been widely confirmed by other investigators, who have also pointed out the highly specific nature of this antagonism, atropine being ineffective against the local and general convulsive activity provoked by other agents (nicotine, strychnine, pentamethylentetrazol, curare, penicillin) (32, 54, 93, 100, 173).

Other contributions come from investigations involving the use of microphysiological techniques. With microelectrophoresis, drugs can be ejected from multibarreled glass micropipettes near neurons from which electrical responses can be recorded. By means of this technique, several cholinoceptive neurons have been identified in various parts of the cerebrum (146). The differential changes in excitability and reactivity of these cells lead to a distinction between nicotinic and muscarinic types, in confirmation of the subdivision already postulated from the relative central activities of certain cholinomimetic and anticholinergic substances (6). The spinal Renshaw cells are, for instance, nicotinic (34), while the cells located in the cerebral cortex are muscarinic (85); ventrobasal thalamic neurons are, according to the results of Andersen and Curtis (5), of an intermediate type. Studies on the effect of atropine on these cells have indicated that the excitation of the cortical muscarinic neurons can be prevented by atropine, either applied by local iontophoresis or administered systemically (1 mg/kg intravenously) (85). On the other hand, its depressive effect on the thalamic and spinal cells could not be considered specific. Sigg *et al.* (152) investigated the effects of cholinergic stimulant and blocking agents, injected into a pial artery, on the cortical axodendritic synapses. Electrical stimulation of the cortical surface evokes a response which, according to Sigg *et al.* (152), is muscarinic in character. The response is diminished by injection of cholinergic agents like acetylcholine, muscarine, or carbachol and is unaffected by nicotine. The diminution of the response provoked by the muscarinic drugs was prevented by atropine.

F. "Dissociation" of behavioral and electroencephalographic effects of anticholinergic drugs

Before this survey is closed, a section must be given over to discussion of a topic in which the two aspects of the central action of anticholinergic drugs meet.

The topic is that of the "dissociation" between the behavioral and EEG effects of anticholinergic drugs. In the first place, note must be made on the origin of this concept, put forth by Wikler in 1952 as a result of his study on the influence of atropine, nalorphine, and morphine on the EEG of unrestrained dogs (182). These observations dealt in particular with the manifestations of motor excitement obtained with atropine, which sometimes existed concomitantly with EEG patterns resembling those of sleep. The conclusions of the author in this connection were that the results suggest "that the spontaneous electrical activity of the cerebral cortex reflects the activity of neuronal systems which, in part at least, are independent of those neuronal systems that subserve behavior in general."

This definition has been so favorably embraced by other investigators that today the word "dissociation" has become a cachet of the central effects of anticholinergic drugs. There has been a tendency, however, to go beyond the interpretation and the conclusions of Wikler, who had clearly indicated the limitations of his statement. One often notes in subsequent investigations related to this matter that, instead of critical attempts to further clarify this concept, many authors have used it as a shield to cover phenomena not easily explainable.

The fact that a great deal of lively discussion has been carried out in the last few years during the course of various symposia and meetings (113, 156), indicates that the problem has matured to a point at which a thorough analysis of all its aspects must be made. The author has discussed at length the "dissociation" in the light of the results obtained in animals prepared with chronically implanted electrodes and trained to perform various kinds of learned task (94). Under these experimental conditions, together with the alterations of the cerebral electrical activity, there is available a better test to measure the sensitivity of the drugged animal to changes in the external environment. With this method Sadowski and Longo (145) could show that in the rabbit, after scopolamine (0.05 to 0.1 mg/kg, intravenously) the disruption of learned, rewarded behavior paralleled the synchronization of the cerebral electrical activity. In further experiments carried out with a different technique, including a discrimination problem, even smaller doses (0.025 mg/kg) altered the behavioral response. At these doses there also appeared a synchronization of the tracing, that had never been noticed in animals performing the simpler exercise. It was therefore possible to show an increased sensitivity of the cerebral electrical activity to the "synchronizing" effects of scopolamine, which was directly related to the influence of the drug on the mechanisms of the correct performance of the response (104). In all the experiments cited above, eserine in doses of 0.05 to 0.15 mg/kg immediately restored the conditioned response together with the EEG patterns of activation. Therefore, from this point of view there appears to be a parallelism, not a dissociation, between the electrical picture and the animal's behavior. Other examples of such parallelism were mentioned by Ricci and Zamparo (137) in their study of the effects of atropine in monkeys trained to an avoidance conditioned response, and by Rougeul *et al.* (143) upon administration of atropine and Ditran (1 to 2 mg/kg subcutaneously) to cats trained to a food reward situation. In cats trained to

light-dark discrimination in a reward exercise, atropine (0.25 to 0.5 mg/kg) provoked the appearance of slow waves in the EEG and increased the latency of performance to a point of no response (89, 151). Similar results on a continuous-intermittent sound discrimination in rabbits were described by Longo (95) after atropine (0.5 mg/kg). Bradley (19) has, however, found that atropine (15 mg/kg) given to rats trained to an avoidance conditioned response led to a "dissociation" between the EEG and behavior. The EEG showed low-frequency high-voltage waves, whereas the performance of the animals was unaffected.

The writer feels that the crucial point, as shown by the pertinent results, lies in the interpretation of the relationships between the cerebral electrical activity and the various forms of integrated motor activity. Undoubtedly, the studies on the central effects of anticholinergic compounds have contributed to elucidate some aspects of this problem. It is clear, for example, that the "synchronization" and the "desynchronization" of the EEG can not be interpreted in terms of "sleep" and "wakefulness." From all the experience gathered from the study of these drugs, it seems that these modifications correspond to alterations of "behavior-related" systems subserving learning, perception and memory.

These data give the concept of "dissociation" new dimensions. Although its application may remain somewhat limited, the formulation of this theory, as often happens in experimental research, has served as a basis for active investigation resulting in both a further clarification of the mechanism of action of anticholinergic drugs and useful hints for future analyses of behavior.

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