ELECTROENCEPHALOGRAPHY
AND
CLINICAL NEUROPHYSIOLOGY
AN INTERNATIONAL JOURNAL

Vol. 9, Number 2 May 1957

THE EFFECT OF CHLORPROMAZINE AND METHOPROMAZINE ON THE ELECTRICAL ACTIVITY OF THE BRAIN IN THE CAT

P. B. BRADLEY, M.D. and A. J. HANCE, B.Sc.[1]
Department of Experimental Psychiatry, Medical School, Hospital Centre, Birmingham, England

(Received for publication: June 4th, 1956)

INTRODUCTION

The central depressant action of chlorpromazine, which has led to its extensive use in the management of chronically over-active psychotic patients (Delay and Deniker 1953; Elkes and Elkes 1954), has been investigated experimentally by a number of workers, many of whom have suggested a possible site of action for this drug. The induction of light sleep in patients receiving chlorpromazine led Terzian (1952) to suggest that the drug might be acting on the brain stem reticular formation, which has been shown by Moruzzi and Magoun (1949), and by Magoun (1952) and his co-workers to influence states of wakefulness in man and in animals. Das, Dasgupta and Werner (1954) injected chlorpromazine intravenously in monkeys and observed changes in the behaviour and EEG. They suggested that the changes which occurred could be explained by a depressant action on the reticular formation of the brain stem rather than an interference with sensory pathways. Other investigators have set out to determine the site of action more specifically. Hiebel, Bonvallet and Dell (1954) have shown that chlorpromazine reduces the cortical response to alerting stimuli (auditory and olfactory), and also to electrical stimulation of the arousal system and the intravenous injection of small quantities of adrenaline. They concluded that the drug depressed the spontaneous activity of the reticular formation and reduced its sensitivity to sensory stimuli. Longo, von Berger and Bovet (1954), working on curarised rabbits and the rabbit *encéphale isolé* preparation, obtained similar results and came to the same conclusion.

With the exception of the experiments by Das *et al.* (1954) on monkeys, all the investigations cited above were carried out on acute preparations in which only electrical responses could be studied. Das *et al.* studied changes in electrical activity of the brain simultaneously with behaviour when administering chlorpromazine, but these experiments were, of necessity, in restrained animals, and in three only were they able to record the EEG before the drug was given. The importance of studying the effect of drugs in conscious chronic preparations in which the electrical activity of the brain and behaviour

[1] Rockefeller Research Scholar.

can be observed simultaneously has been emphasised elsewhere (Bradley and Elkes 1956).

In this study, we have examined the effects of chlorpromazine and methopromazine on the behaviour and electrical activity of the brain in unrestrained conscious animals. We have also used these drugs in combination with other drugs whose effects are well known, and in a limited number of acute preparations.

METHODS

Adult cats, of both sexes, and weighing between 2.5 and 4.0 kg. were used in all experiments.

(*a*) *Conscious Chronic Preparations*

A total of 9 of these preparations has been used. The electrodes were implanted under aseptic conditions employing the technique which has been described previously (Bradley and Elkes 1953a). Experiments were carried out with the animal in a constant environment chamber in which behaviour could be observed through a slit in one wall, whilst the electrical activity was being recorded. This chamber, together with the recording apparatus, was placed in a sound-proofed room. At the beginning of each experiment the animal was allowed a period of acclimatization of 1-2 hours in the chamber before control recordings of electrical activity and an examination of behaviour were made. Observations of affect, sensory responses, motor activity and physiological state were entered on a suitably designed protocol. In this way behaviour observations were standardised for different observers and could be compared from one experiment to another.

In 3 of the chronic preparations a Collison cannula (Feldberg and Sherwood 1953) was implanted in addition to the electrodes, in order that drugs could be injected directly into the ventricles of the brain.

(*b*) *Acute Preparations*

These were the so-called *encéphale isolé* and *cerveau isolé* of Bremer (1935 and 1936) and, in a few experiments, barbitone anaesthetised preparations. The *encéphale isolé* was prepared by transecting the spinal cord at the C_1 level with a blunt leucotome under full ether anaesthesia, and the *cerveau isolé* by transection of the mid-brain at the intercollicular level. The latter operation was usually carried out by aspiration of brain tissue with a fine pipette, under direct vision through a hemicraniotomy. The opposite hemisphere was then used for electrical recordings. The femoral vein was cannulated routinely for the injection of drugs and either the femoral or carotid artery for the recording of blood pressure. This recording was made either on a kymograph using a mercury manometer, or on the same record as the electrical activity by means of an electronic manometer.

The electrodes used for recording the electrical activity of the brain in the acute preparations were identical with those implanted in the chronic preparations. The use of these did not involve exposure of the surface of the cortex and hence no special precautions as to control of temperature and dehydration were necessary. All recordings were made on Edison Swan portable four-channel recording equipment.

(*c*) *Drugs*

The drugs used were, as far as possible, prepared freshly for each experiment by dissolving the pure substance in sterile distilled water. In some cases manufacturers' solutions were used. The drugs employed were: Chlorpromazine hydrochloride, 4560 R.P., Methopromazine acid maleate, 4632 R.P. (May & Baker, Ltd.); r-Amphetamine sulphate (Menley & James, Ltd.); d-Lysergic acid diethylamide (LSD 25) (Sandoz Products, Ltd.); Atropine sulphate, Physostigmine sulphate, Ephedrine hydrochloride (British Drug Houses, Ltd.); Neostigmine methylsulphate (Roche Products, Ltd.); l-*nor*-Adrenaline bitartrate (Bayer Products, Ltd.).

RESULTS

(*a*) *In the conscious animal*

The electrical activity of the brain in the unrestrained conscious cat has been described previously (Bradley 1952; Bradley and Elkes 1956). This activity in the normal animal, correlates closely with the behavioural state. In the experiments described here, when the animals were left undisturbed they became drowsy and in some cases appeared to be asleep, often curled up in a characteristic

way. In this state, the electrical activity consisted of slow waves, often of large amplitude, together with bursts of spindles at 9-12 c/sec. (fig. 1 A). Suitable stimuli (auditory or tactile) caused an arousal or alerting response (Rheinberger and Jasper 1937), in which the cat lifted its head and opened its eyes, and in some cases rose to its feet. At the same time, the slow waves in the electrocorticogram were blocked and only low voltage fast activity at 15-30 c/sec. remained. This has been called the "alert" type of pattern and the slow waves and spindles have been called the "drowsy" pattern. If, after an arousal had been obtained, the animal was left undisturbed, it would usually return to the drowsy state and there was a corresponding change in the electrical activity. In some animals during this transition, bursts of rhythmic 5-8 c/sec. waves appeared in the electrocorticogram which have been associated with an intermediate, "quiet" behavioural state (fig. 1 B).

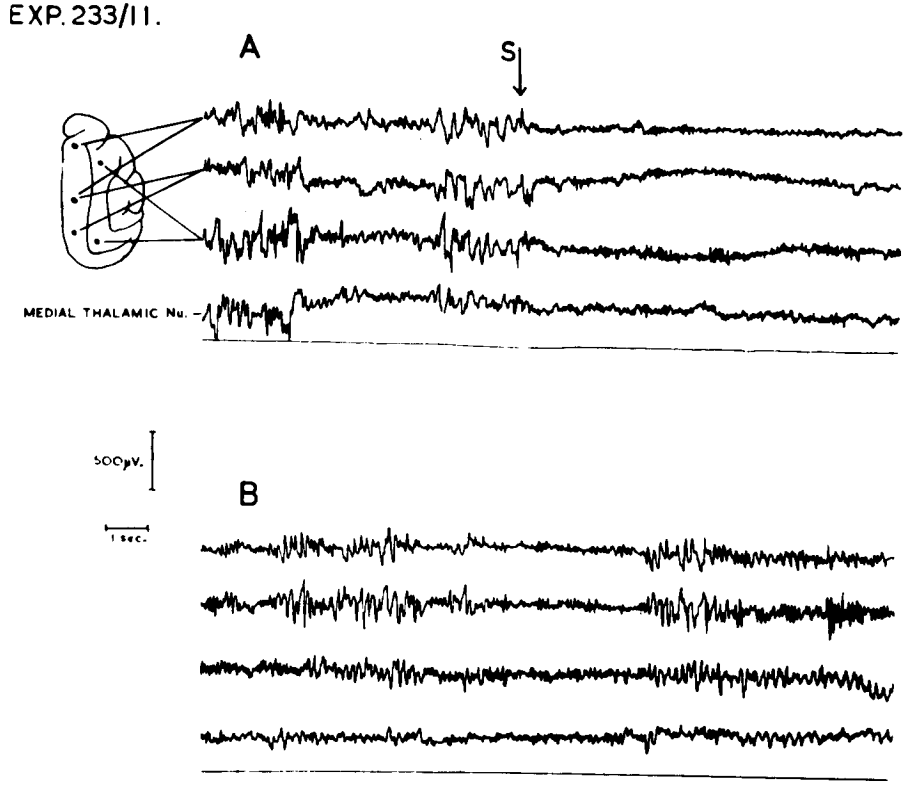

Fig. 1

Typical records of the electrocortical activity of a normal conscious cat in different behavioural states.

A. Arousal from the drowsy state through a sensory stimulus (noise) at "S".

B. Quiet.

(i) *Chlorpromazine*

This drug was used either alone or in combination with other drugs in a total of 68 experiments in conscious chronic preparations and in 36 of these experiments it was the first drug to be given. Consistent changes in the behaviour and in the electrical activity of the brain were observed with doses of 15 to

20 mg/kg. by intraperitoneal injection and 3.0 to 4.0 mg/kg. intravenously. The animals, which had been previously friendly or affectionate, became indifferent both to the environment and to the observer, and in 9 experiments were slightly aggressive when disturbed. Following chlorpromazine some ataxia was noted. The animals were unable to rise, stimuli (pinching the tail or paws) unless such stimuli were prolonged. Relaxation of the nictitating membrane was always observed, and in 13 experiments slight dilation of the pupils occurred. There was little change in the rate of respiration.

The electrical activity of the cortex reflected the changes in behaviour induced by

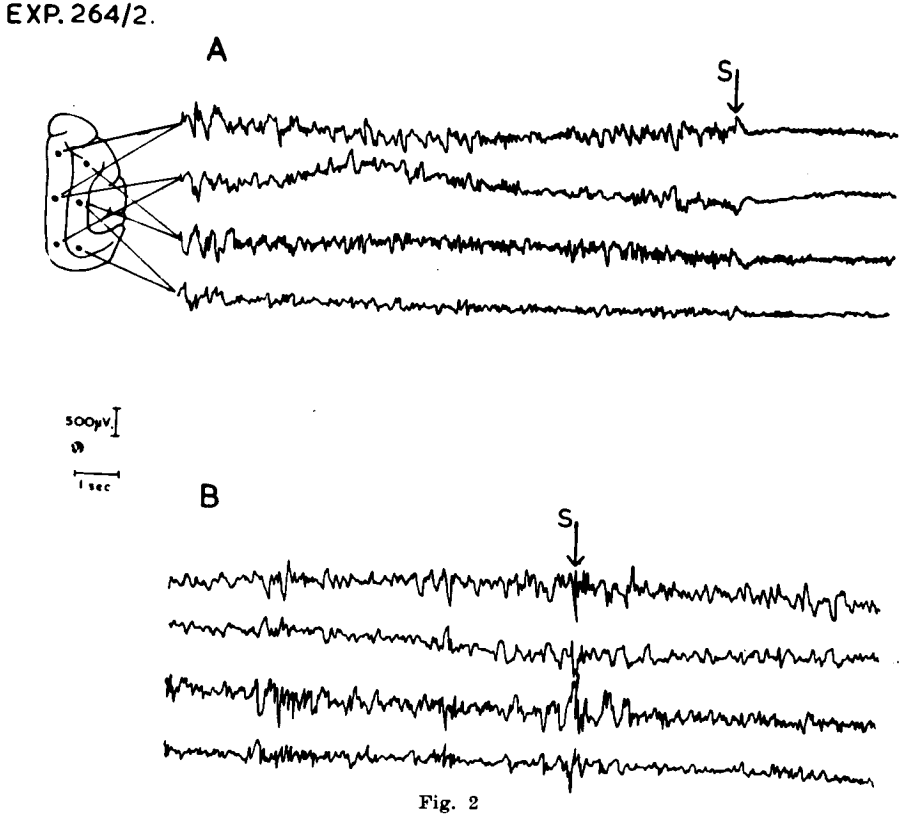

Fig. 2

Records from an experiment in a chronic preparation in which chlorpromazine was given by the intraperitoneal route.

A. Control record of the conscious animal showing arousal from the drowsy state through a sensory stimulus "S".

B. 20 min. after the injection of 15 mg/kg. chlorpromazine hydrochloride intraperitoneally. An arousal response could no longer be elicited at "S".

and if placed on their feet, they usually made no attempt to walk or remain standing, but sank to the floor immediately. Muscle tone remained unchanged, however. There was no longer any response to auditory, visual or tactile stimuli, and little response to painful the drug. The record was usually dominated by irregular waves at 5-8 c/sec. and with an amplitude of 150-250 μV. (fig. 2 B and 3 B). In one preparation this activity was seen to be more regular and at a slightly higher frequency (9-11 c/sec.) and in other animals,

lower voltage activity at 10-15 c/sec. accompanied the irregular 5-8 c/sec. waves. Slow waves at 2-4 c/sec., varying considerably in amplitude, were also observed. An arousal response could no longer be elicited after chlorpromazine had been given (fig. 2 B), and this was consistent with the absence of a behavioural response. In a few experiments the slow activity was slightly reduced in amplitude for 1 or 2 sec. after the arousal stimulus was given, and in these a slight movement of the head or ears was noted. Alerting of the electrical activity or behaviour was never observed after chlorpromazine had been administered.

The effects of intravenous injections of chlorpromazine (fig. 3 B) were almost identical with those observed with the intraperitoneal route, but the injection of 3.0 - 4.0 mg/kg. of the drug appeared to cause a brief loss of consciousness, lasting for about 1 min. This may have been due to an abrupt fall in blood pressure. There was also a temporary increase in the rate of respiration after intravenous injections.

Recovery from the effects of the drug was complete in 48-72 hours, and within 24 hours the animals were usually feeding normally.

In three preparations chlorpromazine was injected into the lateral ventricles of the brain through an implanted Collison cannula. In these experiments a sterile solution of pure chlorpromazine hydrochloride in distilled water was prepared each time. Following doses of 0.5 mg/kg. the animals were quieter and showed little interest in the environment, whilst the electrical activity consisted of rhythmic waves at 12-15 c/sec. with some slower components. With a total dose of 1.0 mg/kg., ataxia was more marked and there was no longer a response to sensory stimuli. The electrocorticogram showed 3-5 c/sec. irregular waves together with 12 c/sec. activity (fig. 3 C) and an arousal response could no longer be elicited. None of these effects was seen with control injections of distilled water.

(ii) *Methopromazine*

In 7 experiments in conscious chronic preparations methopromazine was injected intraperitoneally in doses of 20-30 mg/kg. The effects on behaviour closely resembled those observed with chlorpromazine; the animals became indifferent and ataxic, and showed no response to sensory stimuli. The nictitating membranes were relaxed, and in one experiment the pupils dilated. In none of these experiments was any change in the rate of respiration observed. However, there were minor differences between the effects of the two drugs. Even after the largest doses of methopromazine (30 mg/kg.) the animals were sometimes restless and in two experiments showed slight aggression when disturbed. A further feature observed with methopromazine was that in all the experiments in which this drug was used, retching and vomiting were noted during the first half hour after its administration; they were not seen with chlorpromazine.

The effects of methopromazine on the electrocortical activity were similar to those of chlorpromazine. In the above doses methopromazine caused irregular 4-7 c/sec. waves to appear together with smaller amplitude 11-14 c/sec. activity, and in most experiments there were some slow waves at 2-3 c/sec. as well. This pattern differed from that induced by chlorpromazine, in that it was interrupted for long periods by low voltage, fast activity, but this was consistent with the greater restlessness of the animals. In spite of the appearance of low voltage fast activity from time to time, the irregular activity, when present, did not respond to arousal stimuli.

(iii) *Combinations of chlorpromazine with amphetamine and lysergic acid diethylamide (LSD 25).*

R-amphetamine sulphate (2.0-5.0 mg/kg. intraperitoneally) and LSD 25 (15-20 μg/kg., intraperitoneally) both produce alerting of electrical activity and behaviour in the normal conscious cat (Bradley and Elkes 1953b, 1956), although their effects differ slightly according to the experimental conditions. In these experiments amphetamine caused the animals to become restless and in some cases excited, whilst the electrical activity was of the type seen in the fully alert animal, i.e. low voltage fast activity at 15-30 c/sec. (fig. 4B).

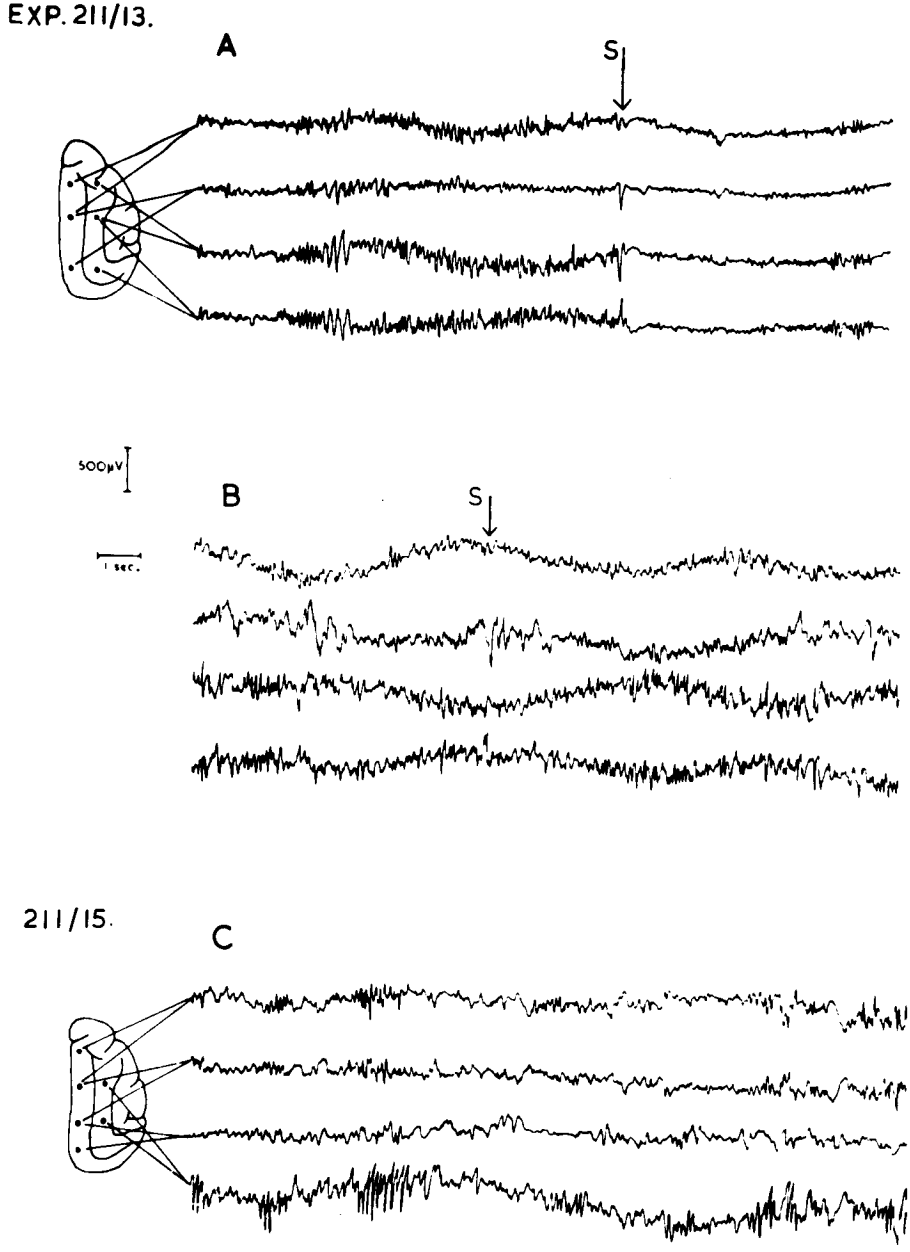

Fig. 3

Records from two separate experiments in the same preparation, in one of which chlorpromazine was given intravenously, and in the other into the lateral cerebral ventricle.

A. Control record showing an arousal response.

B. 16 min. after the injection of 4.0 mg/kg. chlorpromazine hydrochloride intravenously.

C. Another experiment with the same preparation, 16 min. after the injection of 0.6 mg/kg. chlorpromazine hydrochloride into the lateral ventricle of the brain.

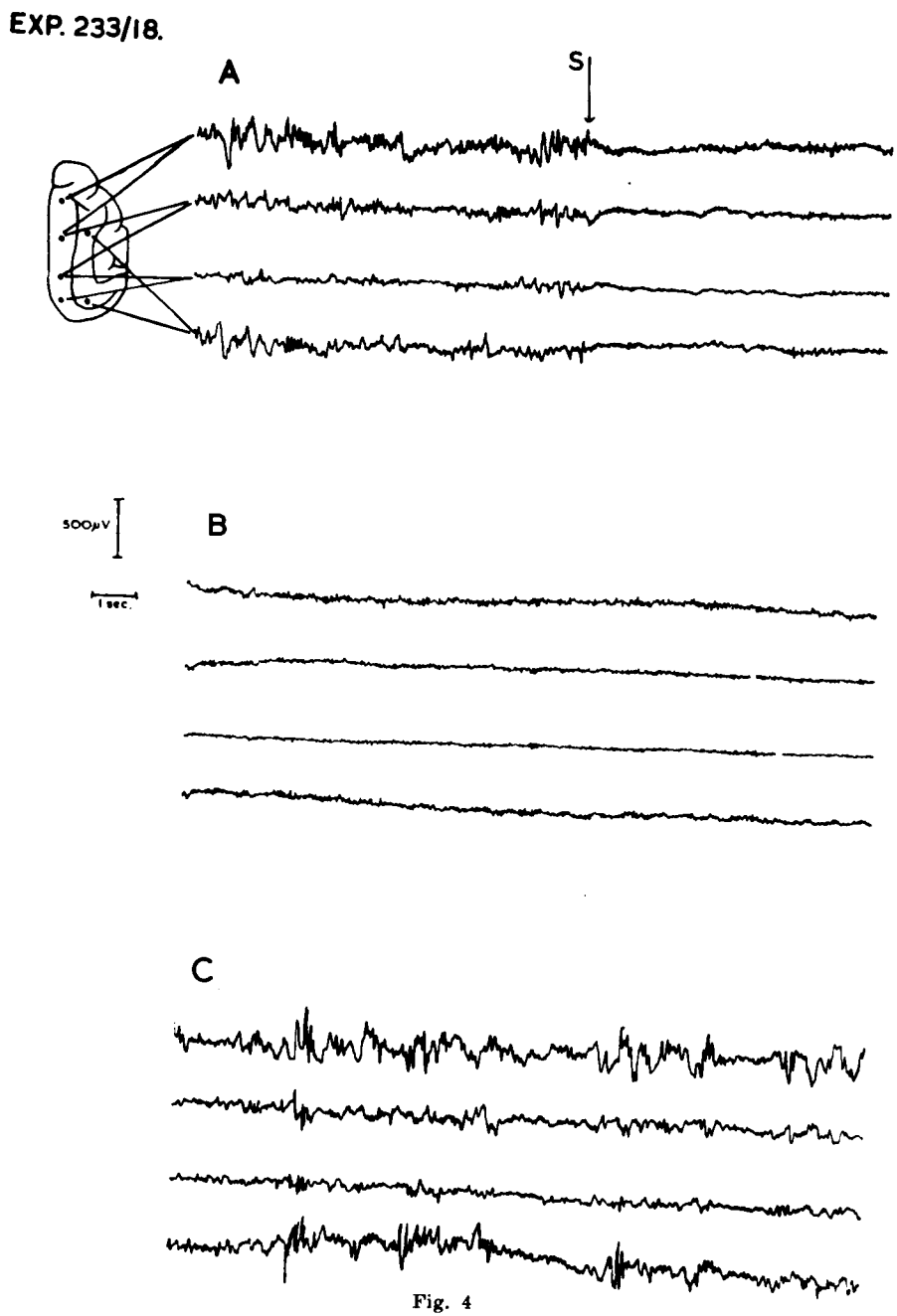

Fig. 4

Records from an experiment in which r-amphetamine was administered to the conscious cat and followed by chlorpromazine.

A. Control record showing arousal.

B. 15 min. after the intraperitoneal injection of 6.0 mg/kg. r-amphetamine sulphate.

C. 35 min. after the subsequent injection of 19 mg/kg. chlorpromazine hydrochloride intraperitoneally.

On the other hand, LSD 25 caused the animals to become more restless and alert, but the electrical activity showed occasional bursts of rhythmic activity at 4-6 c/sec. alternating with the fast low voltage activity of the alert state (fig. 5B). Since these experiments were conducted in a sound-proofed room, extraneous sounds were reduced to a minimum; the influence of the environment in relation to the effects observed with LSD 25 in the conscious animal has been discussed elsewhere (Bradley and Elkes 1956).

Chlorpromazine (15 mg/kg. intraperitoneally) was given after r-amphetamine in 4 experiments and after LSD 25 in another 4. In these experiments chlorpromazine blocked both the behavioural and electrical effects of amphetamine and LSD 25 and produced its own characteristic effects on behaviour and electrical activity (fig. 4C and 5C). In one experiment a larger dose of r-amphetamine (12.5 mg/kg.) was employed and more marked peripheral effects observed. These consisted of dilation of the pupils, salivation, increased respiratory rate, and erection of the fur. With the exception of the pupil dilation, chlorpromazine suppressed all these effects, and produced in the electrocorticogram irregular 5-8 c/sec. activity and slow waves which could not be blocked by the usual arousal stimuli.

In 7 experiments amphetamine was injected after chlorpromazine, but failed to modify either the electrical or behavioural effects of the latter drug even though, in three of these experiments, the doses of amphetamine were increased to 6-12 mg/kg. In another series of 5 experiments LSD 25 was given after chlorpromazine and failed to alter behaviour or the electrocorticogram even when doses of up to 90 μg/kg. were used.

(iv) *Methopromazine and r-amphetamine*

In 2 experiments methopromazine, in doses of 25 mg/kg. (intraperitoneally) was followed by amphetamine. The effects of the latter drug on electrical activity and behaviour failed to appear even when the dose was increased to 10 mg/kg. (intraperitoneally).

(v) *Combinations of chlorpromazine with physostigmine, neostigmine and atropine.*

The effects of physostigmine, neostigmine and atropine on the electrical activity of the brain of the conscious cat have been described (Bradley and Elkes 1953c, 1956). Physostigmine in doses of 0.1-0.4 mg/kg. (intraperitoneally) produces low voltage, fast activity in the electrocorticogram but without alerting of behaviour (fig. 6B). Atropine, on the other hand, in doses of 1.5-3.0 mg/kg. (intraperitoneally) causes the appearance of slow waves similar to those seen in the drowsy or sleeping animal, but in fact does not induce sleep. The slow waves associated with atropine do not respond to arousal stimuli, although the latter produce a normal behavioural response. Thus, with these two drugs there is a dissociation between the electrical activity of the brain and behaviour (Wikler 1952; Bradley and Elkes 1956). Neostigmine has no effect on electrical activity unless doses large enough to produce peripheral effects are used.

Chlorpromazine in doses of 13-30 mg/kg. (intraperitoneally) has been used in combination with physostigmine in 6 experiments. In 4 of these, physostigmine was given first in doses of 0.1-0.4 mg/kg. (intraperitoneally) and it was found that even when the largest doses of chlorpromazine (30 mg/kg.) were used, the low voltage fast activity due to physostigmine persisted, and the electrical patterns characteristic of chlorpromazine failed to appear (fig. 6C). Occasionally short bursts of low voltage activity at 6-7 c/sec. appeared but these were very easily blocked by sensory stimuli. The ataxia, indifference to sensory stimuli and relaxation of the nictitating membrane still appeared and these animals thus presented the behavioural picture characteristic of chlorpromazine, whilst the electrical activity was that associated with physostigmine. In the other 2 experiments in this series, chlorpromazine was administered first and followed by physostigmine. It was found that whereas the ataxia and indifference remained unchanged when physostigmine was injected, the slow and irregular 5-8 c/sec. electrical activity was abolished and replaced by low voltage fast activity (fig. 7c).

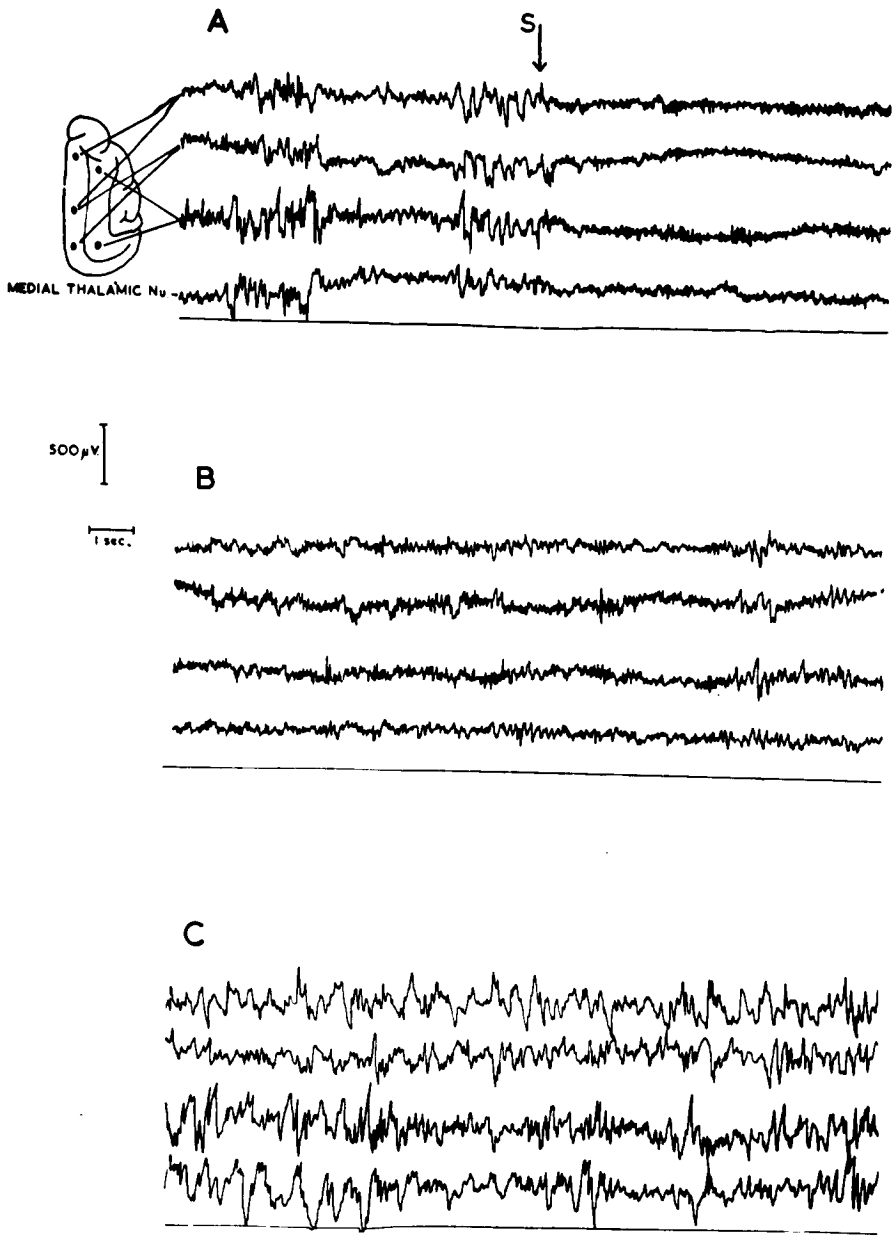

Fig. 5

Records from an experiment in which LSD 25 was given to the conscious animal and followed by chlorpromazine.

A. Control record showing an arousal response.

B. 12 min. after an intraperitoneal injection of 43 μg/kg. LSD 25.

C. 14 min. after the subsequent injection of 18 mg/kg. chlorpromazine hydrochloride intraperitoneally.

Neostigmine in doses of 0.1-0.4 mg/kg. (intraperitoneally) was used in combination with chlorpromazine in 3 experiments. In 2 neostigmine was injected first and in the other it was given after chlorpromazine. In none of these experiments did this drug modify in any way the behavioural and electrical effects induced by chlorpromazine, nor did it block the effects of the latter. The doses of neostigmine used were large enough to produce peripheral effects, increased rate of respiration, bradycardia, increased muscle

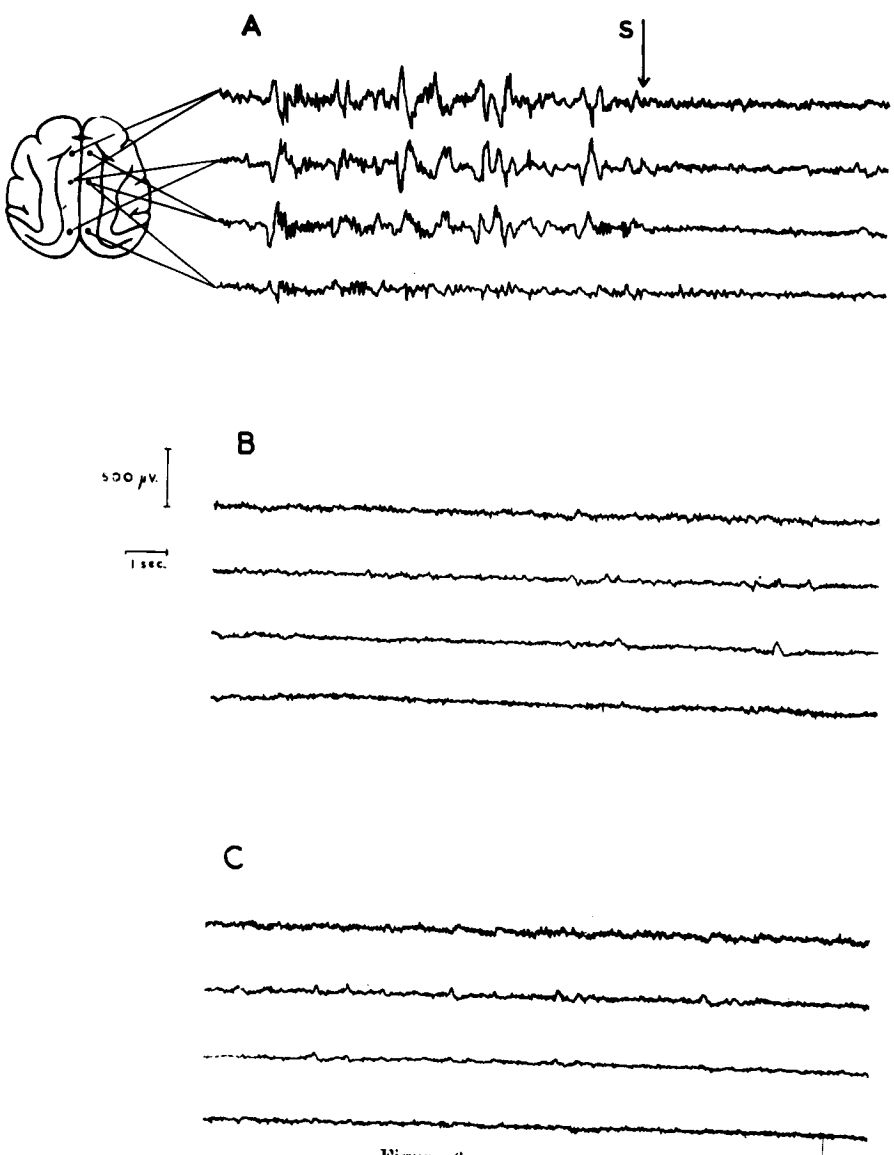

Figure 6

A. Control record of the normal conscious cat showing an arousal response.
B. 14 min. after an intraperitoneal injection of 0.1 mg/kg. physostigmine sulphate.
C. 21 min. after 15 mg/kg. chlorpromazine hydrochloride intraperitoneally.

tone, salivation, vomiting and defaecation. These effects, with the exception of salivation which was suppressed, were not blocked by chlorpromazine.

Atropine was used in combination with chlorpromazine in 12 experiments. The doses of atropine were 0.3-5.7 mg/kg., and those of chlorpromazine 7.4-32.0 mg/kg. In 7 exper-

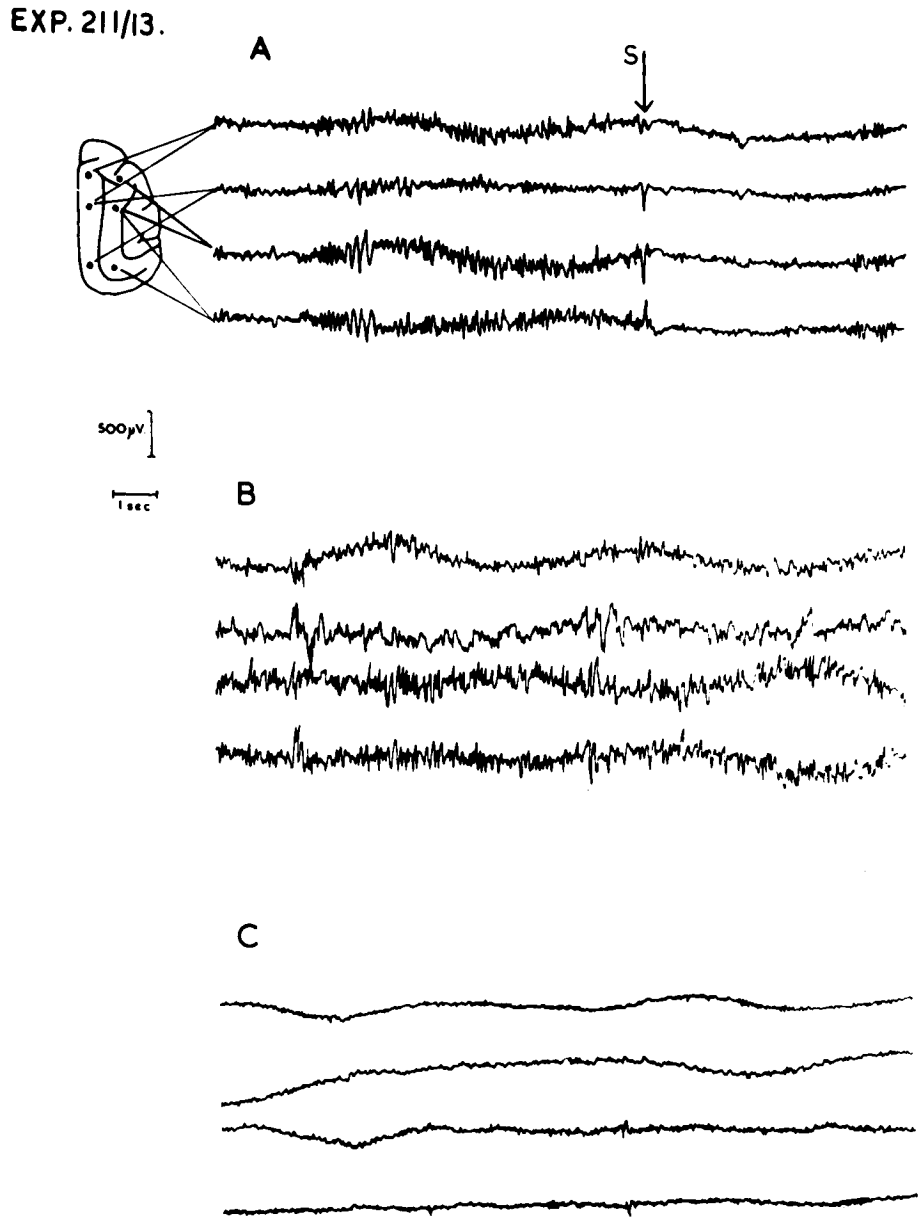

Fig. 7

A. Control record of the normal conscious cat showing an arousal response.
B. 17 min. after an intravenous injection of 4.0 mg/kg. chlorpromazine hydrochloride.
C. 25 min. after 0.2 mg/kg. physostigmine su'phate had been given intraperitoneally.

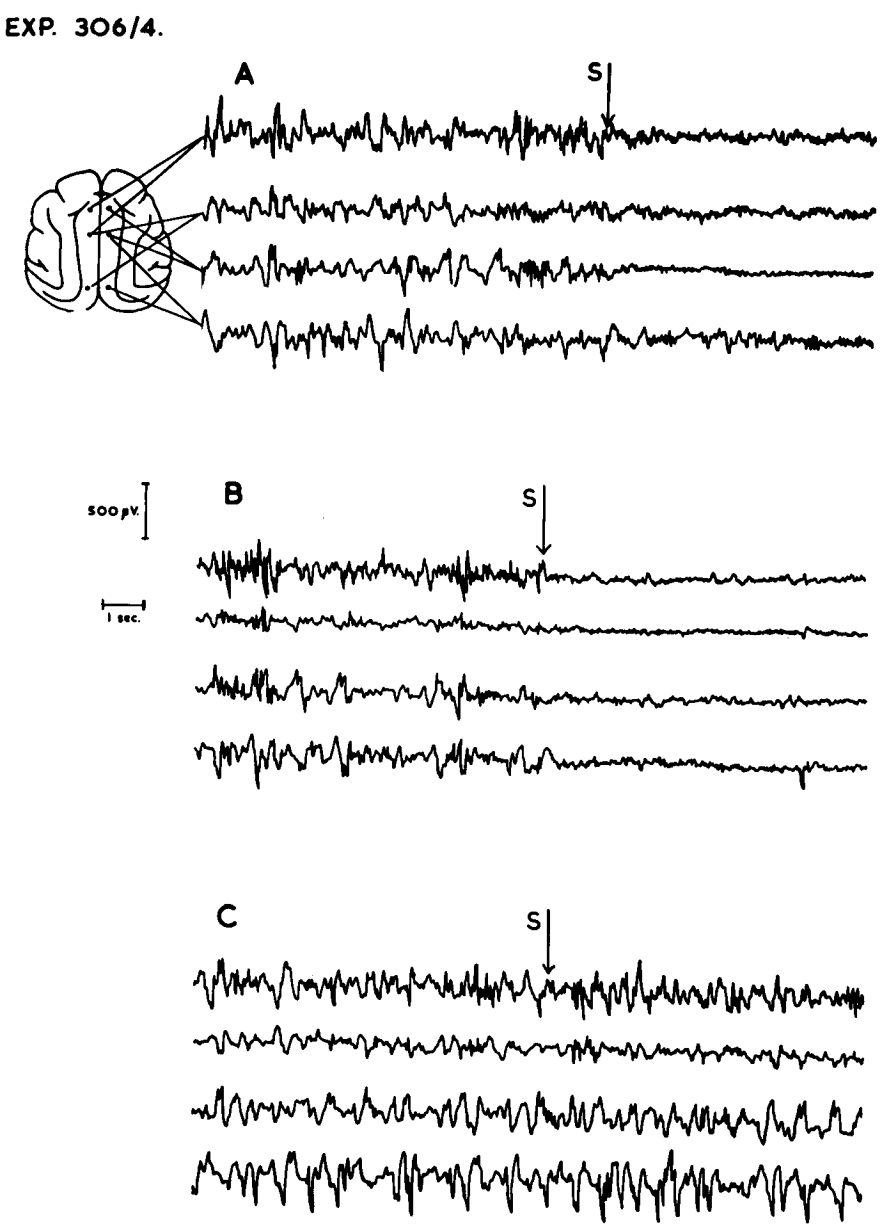

Fig. 8

A. Control record of the normal conscious cat showing an arousal through a sensory stimulus "S".

B. 47 min. after an intraperitoneal injection of 0.3 mg/kg. atropine sulphate, showing that a sensory stimulus "S" still produces an arousal response.

C. 45 min. after 15 mg/kg. chlorpromazine hydrochloride intraperitoneally. The sensory stimulus "S" no longer elicits an arousal response.

iments atropine was administered first, in 5 in doses sufficient to produce slow waves in the electrocorticogram which did not block with sensory stimuli (1.5-3.0 mg/kg.). When chlorpromazine was subsequently injected, it was found that this drug had no effect on the electrical activity, but still produced its usual effects on behaviour, i.e. ataxia and indifference. In the other 2 experiments in which atropine was given first, it was administered in smaller doses (0.3-0.6 mg/kg.). These were insufficient to produce continuous slow activity (fig. 8B), but the latter appeared in the record after chlorpromazine was given (fig. 8C). In 5 experiments in which chlorpromazine was injected first (15-20 mg/kg.) and followed by atropine (0.5-1.2 mg/kg.) the slow activity appeared with smaller doses of atropine than those required to produce a corresponding effect in an animal which had not been treated with chlorpromazine (fig. 9c). The behavioural effects associated with chlorpromazine were however, completely unaffected by the subsequent administration of atropine. As was seen with physostigmine, the behavioural effects here were those associated with chlorpromazine, but the electrical activity of the cortex was that typically seen with atropine.

(vi) *Combinations of methopromazine with physostigmine and atropine.*

In two experiments methopromazine (30 mg/kg.) was followed by physostigmine (0.2 mg/kg.) and atropine (0.5 mg/kg.), respectively. The effects were similar to those observed when these two drugs were used in combination with chlorpromazine. Physostigmine changed the electrical activity to low voltage fast activity and, after the injection of atropine, large amplitude slow waves appeared. In neither case was the behaviour state induced by methopromazine modified in any way. It was found that the dose of atropine required to produce continuous slow waves in the electrocorticogram was smaller when given after methopromazine than that required in the normal animal.

(vii) *Chlorpromazine and sodium pentobarbitone.*

Sodium pentobarbitone was used in 3 experiments with chronic preparations. In one it was given in a dose sufficient to produce mild sedation (7.0 mg/kg.), and in the other 2 to produce a light state of anaesthesia (11.5-18.0 mg/kg.). In the latter state the animals were not fully relaxed and still responded to painful stimuli, whilst the electrocorticogram showed spindle activity at 10-12 c/sec. together with some 6-10 c/sec. activity and slow waves (fig. 10B). With the smallest dose there was only 10-12 c/sec. activity which contained bursts at higher amplitude. In all 3 experiments sensory stimuli or handling caused a brief alerting of the electrical activity.

In these experiments chlorpromazine was subsequently administered in doses of 9.0-20.0 mg/kg. (intraperitoneally). The effect of this drug was to reduce muscle tone and movement but there was no detectable change in the electrical activity of the cortex (fig. 10C). An arousal response could no longer be elicited.

(viii) *Chlorpromazine and ephedrine.*

It was considered that the presence of slow waves in the electrocorticogram following the administration of chlorpromazine might be due to cerebral anaemia resulting from a fall in the blood pressure. Therefore, in 4 experiments, ephedrine in doses between 1.0 and 7.0 mg/kg. was given in an attempt to maintain or raise the blood pressure level. In 2 of these experiments, ephedrine was given first in doses of 2.0-3.0 mg/kg. and its main effects were to cause tachypnoea and pilo-erection. At the same time the electrocorticogram showed an increase in the amount of fast activity present, but this correlated with the behavioural state. Chlorpromazine in doses of 15-20 mg/kg. (intraperitoneally) reduced the respiratory rate and abolished the pilo-erection. It also caused irregular 5-8 c/sec. activity and slow waves to appear in the electrocorticogram and produced its usual ataxia and indifference. In the 2 experiments in which chlorpromazine was injected first (fig. 11B), ephedrine did not modify the behavioural affects produced by this drug and had only a very slight effect on the electrical activity. This consisted of a slight lowering of the amplitude of all frequencies recorded (fig. 11C).

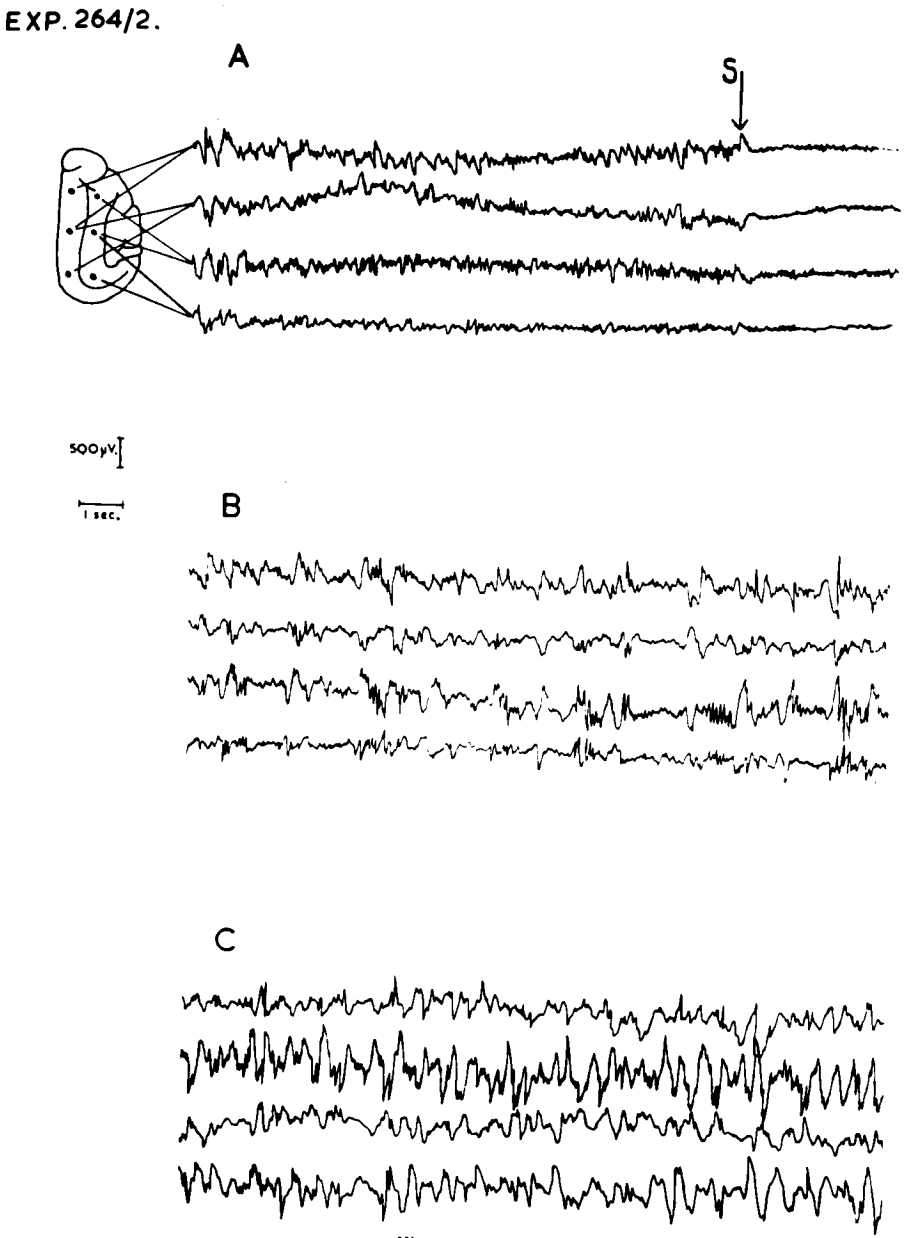

Fig. 9

A. Control record of the normal conscious cat showing an arousal response.
B. 35 min. after 15 mg/kg. chlorpromazine hydrochloride intraperitoneally.
C. 14 min. after the subsequent intraperitoneal injection of 1.2 mg/kg. atropine sulphate.

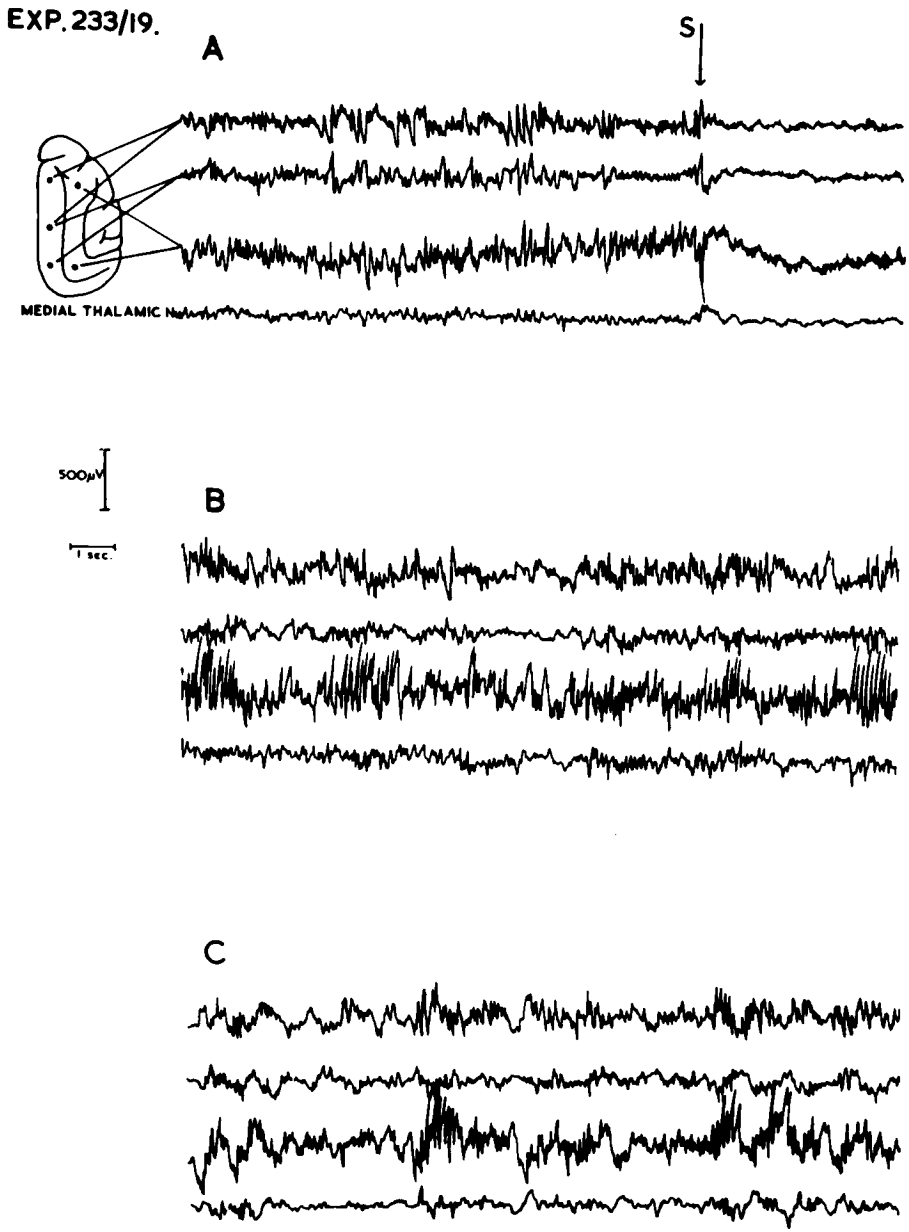

Fig. 10

A. Control record showing an arousal response in the normal conscious cat.
B. 40 min. after an intraperitoneal injection of 11.5 mg/kg. sodium pentobarbitone.
C. 50 min. after a subsequent injection of 21 mg/kg. chlorpromazine hydrochloride intra peritoneally.

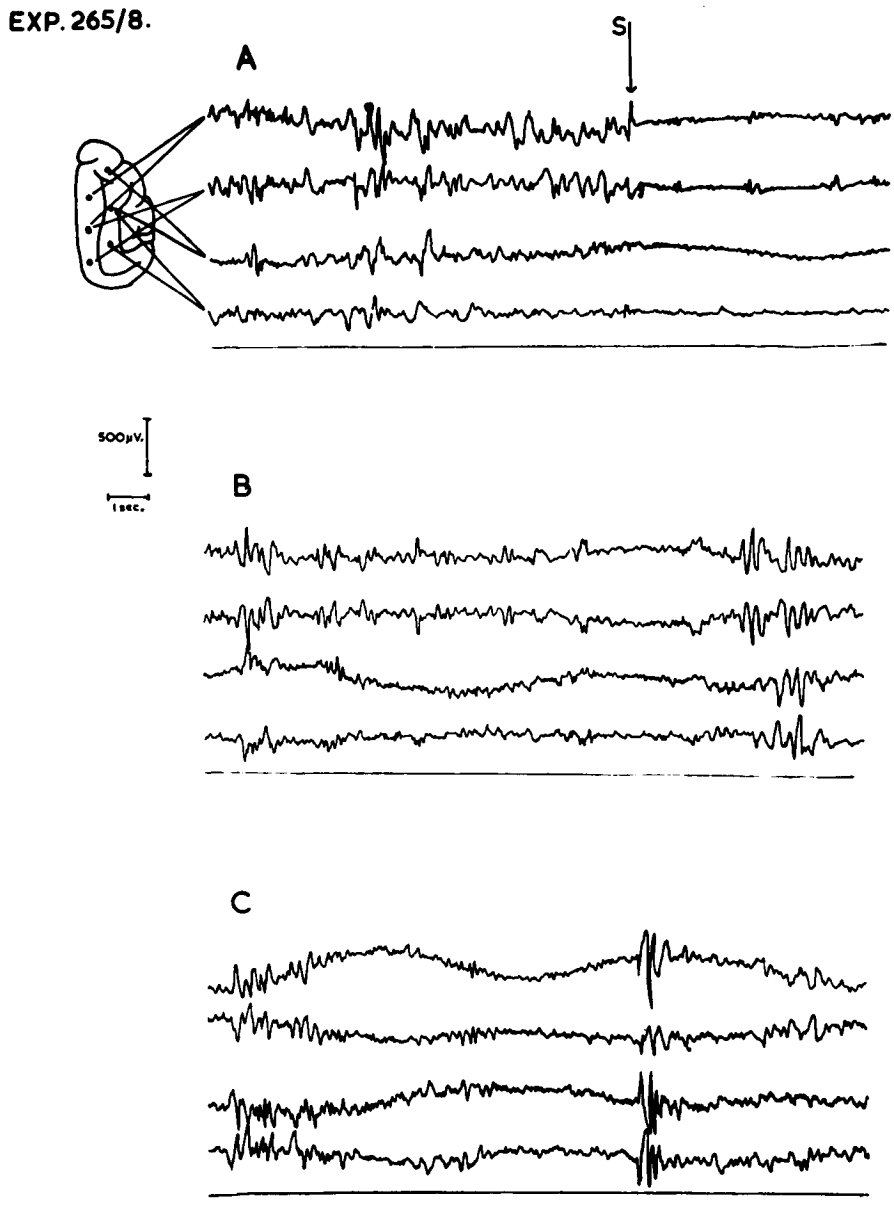

Fig. 11

A. Control record of the normal conscious cat showing arousal.
B. 60 min. after 15 mg/kg. chlorpromazine hydrochloride intraperitoneally.
C. 25 min. after an intraperitoneal injection of 2.0 mg/kg. ephedrine hydrochloride.

(b) *In acute preparations.*

1. *Barbitone anaesthetised preparations.*

In an early series of experiments, 5 cat preparations anaesthetised with sodium pentobarbitone (30-40 mg/kg.) were used, but this type of preparation was later discontinued, as it was found to be unsatisfactory. In these experiments blood pressure was recorded on a kymograph simultaneously with the electrical activity of the brain.

Chlorpromazine, injected intravenously in doses of less than 2.0 mg/kg. had no effect on the electrical activity of the cortex, blood pressure or cardiac rate. The immediate effect of doses greater than 4.0 mg/kg. was to cause a complete flattening of the electrical record corresponding to a sharp fall in the blood pressure of over 50 per cent. After an interval of 1 or 2 min. the blood pressure began to rise again slowly, and eventually slightly exceeded the previous mean before settling down to a constant level. The electrical activity reappeared as the blood pressure rose and consisted at first of rhythmic 6-10 c/sec. waves, followed by 5-7 c/sec. spindles. The only feature which distinguished the record following 4.0 mg/kg. or more of chlorpromazine from that of the animal under pentobarbitone alone, was that the frequency of the spindle activity was reduced from 8-10 c/sec. to 5-7 c/sec. Cardiac rate was unaffected unless doses of chlorpromazine in excess of 12 mg/kg. were used; these produced bradycardia. In 4 experiments *nor*-adrenaline was given as a continuous intravenous infusion, but did not prevent the blood pressure fall and disappearance of electrocortical activity following the intravenous injection of 4.0-13.0 mg/kg. of chlorpromazine.

In one experiment chlorpromazine was injected in divided doses into the lateral ventricle of the brain using a Collison cannula. Although a total dose of 0.6 mg/kg. was injected, no immediate changes in blood pressure or electrical activity were observed. Similarly, no effects were observed when chlorpromazine in doses of 1.5 and 3.5 mg/kg. was injected into the common carotid artery in one of the pentobarbitone anaesthetised preparations.

In one experiment in which 13 mg/kg. of chlorpromazine had been injected intravenously it was followed by 0.9 mg/kg. of physostigmine. The spindle activity was abolished and large amplitude rhythmic activity at 5-7 c/sec. appeared. This activity was similar to that observed with physostigmine alone in the barbitone anaesthetised preparations (Bradley and Elkes 1956).

2. *Encéphale isolé preparations.*

This preparation, in which the spinal cord is transected at the C_1 level (Bremer 1936) provides a means of studying the effects of a drug on the electrical activity of the brain and on blood pressure simultaneously. Since it still responds to arousal stimuli and two states, "sleeping" and "waking", can be distinguished both behaviourally and in terms of electrical activity, this preparation is particularly useful in the study of drugs which affect states of consciousness.

The effects of intravenous injections of chlorpromazine have been studied in eight *encéphale isolé* preparations and were of two types: (*a*) those which occurred in the first few minutes following the injection and were short lived, and (*b*) those which took longer to appear and which persisted throughout the experiment.

When comparatively small doses of chlorpromazine (0.2-1.0 mg/kg.) were injected intravenously, the spindles and slow waves characteristic of the sleeping state in the *encéphale isolé* preparation were either blocked or considerably reduced in amplitude (fig. 12B). The onset occurred between 30 sec. and 3 min. after the injection and the effect lasted for 30-120 sec. During this period the electrical activity consisted mainly of 10-15 c/sec. waves. The injection was usually accompanied by a slight transient rise and fall in blood pressure, but these changes were always complete before the blocking of the slow waves and spindle activity was observed. No changes in the behavioural state of the preparation were seen. Usually this effect was obtained only with the first injection; it was rarely seen with a second injection, even with small doses and it was never observed when doses greater than 1.0 mg/kg. were used.

Different effects were observed with doses in excess of 1.5 mg/kg. It was found that a

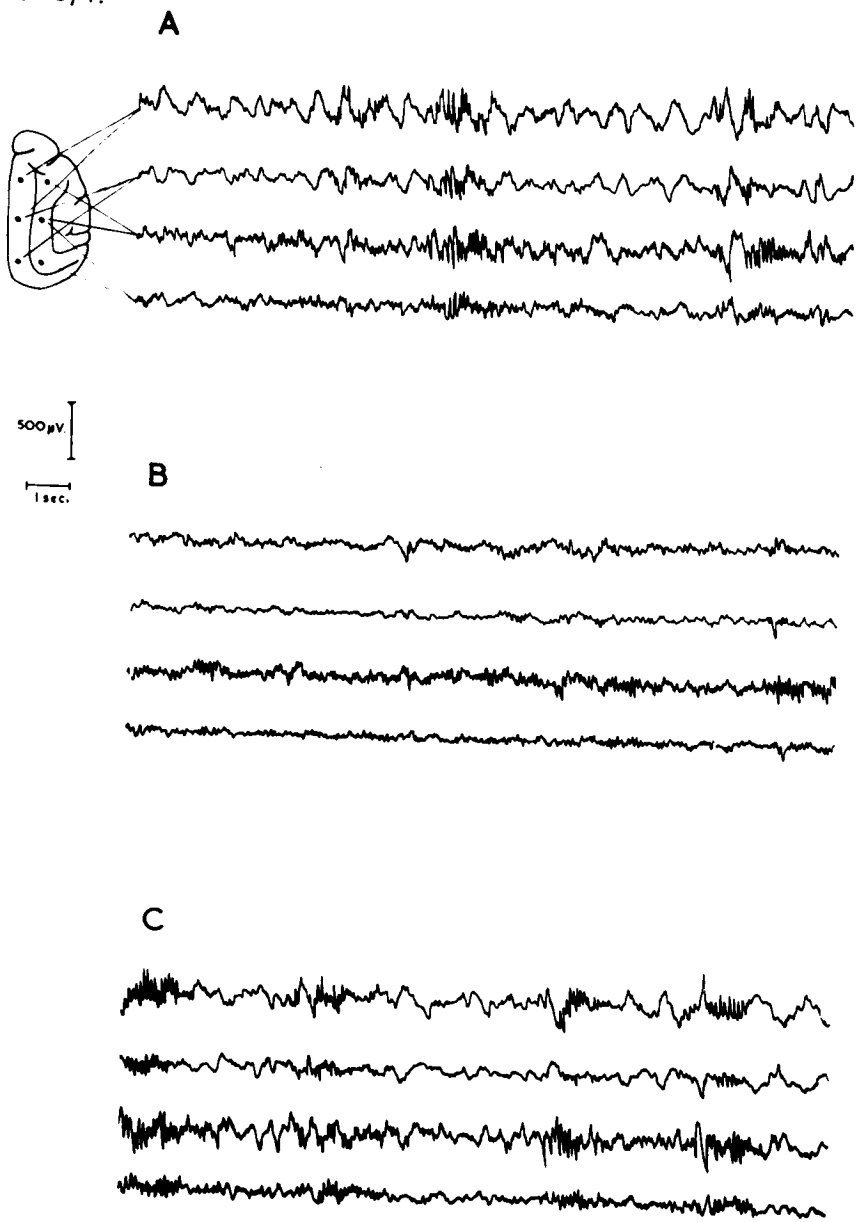

Fig. 12

Records from an acute experiment (*encéphale isolé* preparation) in which a small dose of chlorpromazine was given.

A. Control record with the preparation "sleeping".

B. 30 sec. after 0.5 mg/kg. chlorpromazine hydrochloride had been injected intravenously.

C. 2 min. after the same injection of 0.5 mg/kg. chlorpromazine hydrochloride.

preparation which had previously been easy to arouse by auditory or mild tactile stimuli (applied to the head), could no longer be alerted in this way and proved difficult to arouse even by handling. Slow waves at 1-3 c/sec. were increased in amplitude and were more continuous in the record, and irregular 5-8 c/sec. activity became more marked (fig. 13B). These effects persisted throughout the experiment. The injection of chlorpromazine in doses of 4.0-8.0 mg/kg. (intravenously) caused a fall in blood pressure and a corresponding flattening of the electrocorticogram, followed by a slow recovery similar to that seen with the barbitone anaesthetised preparation.

In two experiments in which *nor*-adrenaline was given as a continuous intravenous drip, it did not modify the effect of chlorpromazine although the mean arterial blood pressure was raised. The slow waves and irregular activity induced by the injection of 1.5-4.0 mg/kg. of chlorpromazine persisted in spite of the high blood pressure, and a further injection of 4.0-8.0 mg/kg. of chlorpromazine still caused a fall in pressure and flattening of the electrocorticogram.

In three experiments, ephedrine was injected intravenously in doses of 2.0-5.0 mg/kg. following chlorpromazine, but although a rise in blood pressure occurred, the electrical activity remained unaltered.

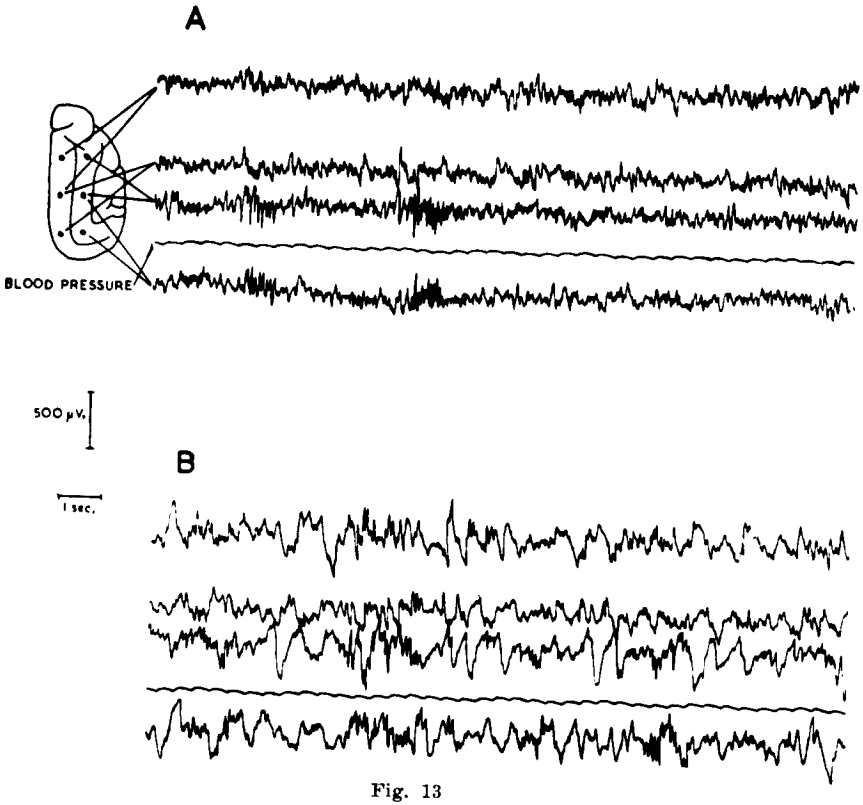

Fig. 13

Records from an acute experiment (*encéphale isolé* preparation).
A. Control record with the preparation "sleeping".
B. 4 min. after the intravenous injection of 2.0 mg/kg. chlorpromazine hydrochloride.

In one experiment in which 8.0 mg/kg. of chlorpromazine had been injected, it was followed by r-amphetamine in a dose of 16 mg/kg. The latter had no effect on the slow wave and spindle activity, although in the normal *encéphale isolé* it is effective in much smaller doses (1.5-3.0 mg/kg.). In this same preparation and in two others, 0.2 mg/kg. of physostigmine was subsequently injected and blocked both the slow waves and the spindle activity.

In a further three *encéphale isolé* preparations, in which a Collison cannula together with recording electrodes was inserted into the skull, chlorpromazine was injected into the lateral ventricle in doses of 0.25-4.0 mg/kg. In two of these experiments no change in electrical activity was observed, but in the third the slow waves and spindle activity became more pronounced. These doses of chlorpromazine were also found to block the blood pressure rise caused by an intravenous injection of 5-40 μg. of adrenaline.

3. *Cerveau isolé preparations.*

The effects of chlorpromazine were examined in 8 preparations of this type. In 4 the mesencephalic section was at the intercollicular level, passing rostrally to the sella turcica, and in the other 4 the section was slightly more caudal. In all except one, in which only a unilateral transection was made, the cortical activity consisted of slow waves or spindles and an arousal response could not be obtained. Chlorpromazine in doses of 0.2-2.0 mg/kg. had no effect on the electrocortical activity of these preparations and only the slight rise and fall in blood pressure associated with the injection was observed. In the preparation in which only a unilateral transection of the mid-brain had been performed, the effects following the injection of 0.5 mg/kg. of chlorpromazine were similar to those observed with small doses in the *encéphale isolé*, namely a transient blocking of the slow waves and spindle activity, lasting for about 60 sec. This preparation behaved in much the same way as an *encéphale isolé* preparation before chlorpromazine was injected, and it responded both behaviourally and electrically to arousal stimuli.

Doses of chlorpromazine in excess of 5.0 mg/kg. caused a pronounced fall in blood pressure and a flattening of the electrocortical activity similar to that observed when doses of this order were used with the *encéphale isolé* and barbitone anaesthetised preparations. In one experiment, however, this effect was observed with a dose of 0.2 mg/kg.

DISCUSSION

The results of the experiments described above are summarised in table I. The effects produced by chlorpromazine alone in the conscious unrestrained cat seemed to be independant of the route by which the drug was given, but there were marked differences in the doses required. Similar effects were produced by 0.5-1.0 mg/kg. intraventricularly, 3.0-4.0 mg/kg. intravenously, 15-20 mg/kg. intraperitoneally and 20-30 mg/kg. intramuscularly. These are in agreement with the general range of doses used by other workers. For example, Courvoisier *et al.* (1953) found that 10 mg/kg. was necessary to produce locomotor difficulty in dogs when given subcutaneously, and Boyd *et al.* (1953) used up to 40 mg/kg. orally. The intraperitoneal route, which was found to be the most convenient for repeated injections in the conscious cat, was used in most of our experiments, and accounts in some measure for the large doses employed. In all these experiments full recovery occurred within 48 to 72 hours and, despite repeated injections of chlorpromazine (and other drugs), the animals remained healthy and no change in their demeanour or behaviour was observed.

The effects which we observed with chlorpromazine in the conscious unrestrained cat are in close agreement with the findings of Das, Dasgupta and Werner (1954) in the conscious monkey. In all their experiments chlorpromazine was injected intravenously and they found that doses between 0.7 and 2.0 mg/kg. were required. We have had an opportunity to inject chlorpromazine intravenously into a number of monkeys and observe their behaviour. We found that in these animals, doses of 1.5 mg/kg. or less, frequently caused drowsiness. There would therefore appear to be a species difference

TABLE I

Drug	*Conscious Animal*		*Encéphale Isolé*	*Cerveau Isolé*	*Effects of Other Drugs After Chlorpromazine*	
	Behaviour	*Electrical Activity*	*Electrical Activity*	*Electrical Activity*	*Behaviour*	*Electrical Activity*
Chlorpromazine	Drowsiness and indifference	Slow and 5-8 c/sec. activity	Increased slow activity and spindles	No effect		
Physostigmine	Normal	Fast, low amplitude activity	Fast, low amplitude activity	Fast, low amplitude activity	No effect	Fast, low amplitude activity
Atropine	Normal or excited	High amplitude slow waves and spindles	High amplitude slow waves and spindles	High amplitude slow waves and spindles	No effect	High amplitude slow waves and spindles
Amphetamine	Excited	Fast, low amplitude activity	Fast, low amplitude activity	No effect	No effect	No effect
LSD 25	Excited	Fast, low amplitude activity	No effect	No effect	No effect	No effect

between the cat and monkey in terms of the effective intravenous dose of chlorpromazine.

It seems unlikely for a number of reasons that, with the exception of the immediate effects of the intravenous injections, the effect of chlorpromazine in the conscious animal was due to any depression of blood pressure by the drug. Firstly, in experiments on the anaesthetised dog, Courvoisier *et al.* (1953) found that intravenous injections of 1.0-5.0 mg/kg. had little effect on blood pressure, and our own experiments on barbitone anaesthetised preparations and on the *encéphale isolé* confirm this. When large enough doses to cause a blood pressure fall were used, the latter was usually transient, whereas the effects of chlorpromazine in the conscious animal persisted. Secondly, no change in blood pressure was observed by Cathala and Pocidalo (1952) when they injected 2.0 mg/kg. of the drug into the lateral ventricles although ataxia was produced. Our own experiments in which chlorpromazine was injected intraventricularly, both in the conscious animal and in the *encéphale isolé*, confirm this. Thirdly, the injection of ephedrine, either before or after chlorpromazine, did not block or modify the effects of this drug, although ephedrine still produced a rise in blood pressure when injected after chlorpromazine in the *encéphale isolé*. These facts lend support to the suggestion that the effects on behaviour and electrical activity of the brain observed with chlorpromazine in the conscious animal are due to a direct action by the drug on the central nervous system. This is further supported by the observation that intraventricular injections of chlorpromazine in the *encéphale isolé* blocked the pressor response to adrenaline.

Methopromazine produced effects similar to those which were observed with chlorpromazine, but the effects both on behaviour and on electrical activity were less marked in spite of the larger doses used. This compound, which differs from chlorpromazine only by the presence of a methoxy ($-OCH_3$) group instead of a chlorine atom on the phenothiazine nucleus (Charpentier *et al.* 1952), is reported to have similar pharmacological properties to chlorpromazine, although in some tests it was slightly less effective (May and Baker 1955). The difference between the effective doses of chlorpromazine and methopromazine in our experiments cannot be accounted for by the difference in the molecular weights of the salts in relation to the base (chlorpromazine being the hydrochloride and methopromazine the acid maleate). Thus, in terms of its central depressant effect, methopromazine would appear to be slightly weaker than chlorpromazine, as suggested by the difference in the doses required and by the qualitative differences in the effects.

In our experiments, chlorpromazine had no effect on the *cerveau isolé* preparation provided the midbrain transection was complete, and provided the doses used were insufficient to cause a marked drop in blood pressure. Das, Dasgupta and Werner (1955) have reported that small doses (0.2 mg/kg.) were sufficient to block the slow waves and spindles in this preparation. However, they do not say whether there was any corresponding change in blood pressure. In one of our experiments with this preparation we obtained a marked blood pressure fall with 0.2 mg/kg. and a corresponding blocking of cortical activity. In another preparation in which the midbrain transection was unilateral, the slow waves and spindles were temporarily blocked when chlorpromazine was injected. The effects obtained by Das, Dasgupta and Werner could therefore be due to either a change in the blood pressure level or an incomplete transection.

In our experiments, chlorpromazine had an effect on the intact animal and the *encéphale isolé*, but not on the *cerveau isolé* (table I). This suggests that the drug might be exerting its influence on some structure situated between the two planes of section of the acute preparations, i.e. between the upper spinal cord and the mesencephalon. This corresponds to the region in which the brain stem reticular activating system has been located (Magoun 1952) and is also the region which, for different reasons, has been suggested as the site of action of chlorpromazine by other workers (Terzian 1952; Hiebel *et al.* 1954; Longo *et al.* 1954). Further support for this suggestion comes from the results of the experiments in which chlorpromazine was used in combination with other drugs. The

effects of amphetamine and LSD 25, both on behaviour and electrical activity of the brain, were completely blocked by chlorpromazine. There is strong evidence to suggest that amphetamine, and possibly LSD 25 as well, produce their effects by an action on receptors situated at the level of the brain stem (Bradley and Elkes 1953b, 1956). The facts that neither chlorpromazine nor amphetamine have any effect on the *cerveau isolé* preparation and that chlorpromazine blocks the effects of amphetamine, both in the intact animal and in the *encéphale isolé,* support the suggestion that chlorpromazine exerts its depressant effect on the arousal system. The recent suggestion (Bonvallet, Dell and Hiebel 1954) that this system may contain an adrenergic element might form a possible link between the central depressant action and the anti-adrenaline action of chlorpromazine. The results of our experiments with intraventricular injections of this drug in the *encéphale isolé* indicate that the antagonism to the adrenaline pressor response may be a central effect.

When chlorpromazine was used in combination with atropine and physostigmine, it was noticed that these drugs still produced their characteristic effects on electrical activity, but the behavioural effects of chlorpromazine predominated. However, atropine and physostigmine produce effects on electrical activity in the conscious animal which are unrelated to behaviour and also influence the electrical activity of the *cerveau isolé* (Bradley and Elkes 1953c, 1956). This led us to suggest that it is unlikely that these drugs act on the brain stem reticular formation in producing the effects observed and that this system is probably not predominantly cholinergic. If chlorpromazine does act on the reticular formation and these drugs do not, then it might be expected that they would modify electrical activity whilst the behavioural effects of chlorpromazine persisted.

There seemed to be some synergism between the electrical effects of atropine and chlorpromazine since, when the latter drug was given, the doses of atropine required were from 5-10 times smaller than those needed for comparable effects in the untreated animal. This was independent of the order in which the drugs were given. It may possibly be related to the anti-acetylcholine properties of chlorpromazine which, though weak, have been measured peripherally (Kopera and Armitage 1954).

It is interesting to note that small quantities of chlorpromazine injected intravenously in the *encéphale isolé* preparation appeared to have a stimulating effect, since the sleep activity of this preparation was temporarily blocked. This effect was unrelated to changes in blood pressure and was not observed with larger doses, or with subsequent injections. It would appear that whilst the main action of chlorpromazine may be a central depression, in small doses it may have some excitatory effect. The depressant effect may take longer to appear, especially when smaller doses are used, and therefore the excitatory effect would be seen only with the first injection and with small doses.

The precise mechanism underlying the central depressant action of chlorpromazine is still a subject for speculation. It is known to have marked anti-adrenaline properties both peripherally (Courvoisier *et al.* 1953) and centrally (Hiebel *et al* 1954), and recently it has been shown to antagonise 5-hydroxytryptamine both *in vivo* and *in vitro* (Benditt and Rowley 1956). Both of these substances have recently been identified in the brain, and in higher concentrations in the hypothalamus and brain stem (Vogt 1954; Amin *et al* 1954). More recently Wase, Christensen and Polley (1956) have shown that chlorpromazine labelled with radioactive sulphur (S^{35}) accumulated in the hypothalamus. These observations, together with the results of the experiments described here, strongly support the hypothesis that chlorpromazine depresses the arousal system situated at the level of the brain stem, and it may do so by interfering with a system pharmacologically related to a centrally acting catechol amine.

SUMMARY

1. The effects of chlorpromazine and methopromazine on the electrical activity of the brain and on behaviour have been studied in the conscious unrestrained cat. Both produced ataxia and indifference together with slow and irregular 5-8 c/sec. waves in the electrocorticogram. These effects were less

marked with methopromazine. With chlorpromazine the effects seen were independent of the route used, but different doses were required.

2. Both drugs blocked the effects on behaviour and electrical activity which are normally observed with amphetamine and LSD 25. Atropine and physostigmine still produced their characteristic effects on electrical activity but did not modify the behavioural state induced by chlorpromazine or methopromazine.

3. Chlorpromazine in doses of 1.5-4.0 mg/kg. produced an increase in the slow waves and spindle activity in the *encéphale isolé* preparation and at the same time made the preparation more difficult to arouse. Smaller doses produced a transient blocking of this activity with the first injection, but larger doses caused a blood pressure fall and flattening of the record. Chlorpromazine had no effect on the *cerveau isolé* preparation other than the effects associated with a fall in blood pressure.

4. The results are discussed in relation to the planes of section of the two acute preparations and the possible sites of action of the other drugs used. It is suggested that chlorpromazine has a depressant action on the brain stem reticular system and that this action may be related to its anti-adrenaline properties. It is further suggested that small doses have an excitatory action which can only be observed before the depressant action has appeared.

We wish to thank Professor J. Elkes for his advice and encouragement, M. Longmore and L. F. Williams for technical assistance, Messrs. May and Baker for providing Methopromazine and Chlorpromazine, and Messrs. Sandoz Products Ltd. for supplies of LSD 25.

REFERENCES

AMIN, A. H., CRAWFORD, T. B. B. and GADDUM, J. H. The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *J. Physiol.*, **1954**, *126*: 596-618.

BENDITT, E. P. and ROWLEY, D. A. Antagonism of 5-hydroxytryptamine by chlorpromazine. *Science*, **1956**, *123*: 24.

BONVALLET, M., DELL, P. et HIEBEL, G. Tonus sympathique et activité électrique corticale. *EEG Clin. Neurophysiol.*, **1954**, *6*: 119-144.

BOYD, E. M., CASSELL, W. A. and BOYD, C. E. Prevention of apomorphine-induced vomiting by (dimethylamino-1-n-propyl-3)-N-(2-chloro)-phenothiazine hydrochloride. *Fed. Proc.*, **1953**, *12*: 303.

BRADLEY, P. B. Observations on the effect of drugs on the electrical activity of the brain. Ph.D. thesis, University of Birmingham, **1952**.

BRADLEY, P. B. and ELKES, J. A technique for recording the electrical activity of the brain in the conscious animal. *EEG Clin. Neurophysiol.*, **1953**a, *5*: 451-456.

BRADLEY, P. B. and ELKES, J. The effect of amphetamine and *d*-lysergic acid diethylamide (LSD 25) on the electrical activity of the brain of the conscious cat. *J. Physiol.*, **1953**b, *120*: 13-14 P.

BRADLEY, P. B. and ELKES, J. The effect of atropine, hyoscyamine, physostigmine and neostigmine on the electrical activity of the brain of the conscious cat. *J. Physiol.*, **1953**c, *120*: 14-15 P.

BRADLEY, P. B. and ELKES, J. The effect of some drugs on the electrical activity of the brain. *Brain*, **1956**, in press.

BREMER, F. Cerveau "isolé" et physiologie du sommeil. *C. R. Soc. Biol.*, Paris, **1935**, *118*: 1235-1241.

BREMER, F. Nouvelles recherches sur le mécanisme du sommeil. *C. R. Soc. Biol.*, Paris, **1936**, *122*: 460-464.

CATHALA, H. P. et POCIDALO, J. J. Sur les effets de l'injection dans les ventricules cérébraux du chien du chlorohydrate de diméthylamino-propyl-N-chloro-phénothiazine (4560 RP). Action centrale de ce produit. *C. R. Soc. Biol.*, Paris, **1952**, *146*: 1709-1711.

CHARPENTIER, P., GAILLIOT, P., JACOB, R., GAUDECHON, J. et BUISSON, P. Recherches sur les diméthylaminopropyl-N-phénothiazines substituées. *C. R. Acad. Sci.*, Paris, **1952**, *235*: 59-60.

COURVOISIER, S., FOURNEL, J., DUCROT, R., KOLSKY, M. et KOETSCHET, P. Propriétés pharmacodynamiques du chlorohydrate de chloro-3-diméthylamino-3'-propyl)-10-phénothiazine (4560 RP); étude expérimentale d'un nouveau corps utilisé dans l'anesthésie potentialisée et dans l'hibernation artificielle. *Arch. int. Pharmacodyn.*, **1953**, *92*: 305.

DAS, N. N., DASGUPTA, S. R. and WERNER, G. Changes of behaviour and electro-encephalogram in rhesus monkeys caused by chlorpromazine. *Arch. int. Pharmacodyn.*, **1954**, *99*: 451.

DAS, N. N., DASGUPTA, S. R. and WERNER, G. The effects of chlorpromazine on the electrical activity of the "cerveau isolé". *Arch. exp. Path. Pharmak.*, **1955**, *224*: 248-252.

DELAY, J. et DENIKER, P. Les neuroplégiques en thérapeutique psychiatrique. *Thérapie*, **1953**, *8*: 347.

ELKES, J. and ELKES, C. Effect of chlorpromazine on the behaviour of chronically overactive psychotic patients. *Brit. med. J.*, **1954**, *ii*: 560-565.

FELDBERG, W. and SHERWOOD, S. L. A permanent cannula for intraventricular injections in cats. *J. Physiol.*, **1953**, *120*: 3-5 P.

HIEBEL, G., BONVALLET, M. et DELL, P. Action de la chlorpromazine (Largactil, 4560 RP) au niveau

du système nerveux central. *Sem. Hôp.* Paris, **1954**, *30*: 2346-2353.

KOPERA, J. and ARMITAGE, A. K. Comparison of some pharmacological properties of chlorpromazine, promethazine and pethidine. *Brit. J. Pharmacol.*, **1954**, *9*: 392-401.

LONGO, V. G., VON BERGER, G. P. and BOVET, D. Action of nicotine and of the "ganglioplégiques centraux" on the electrical activity of the brain. *J. Pharmacol. exp. Therap.*, **1954**, *111*: 349-359.

MAGOUN, H. W. The ascending reticular activating system. *Res. Publ. Ass. nerv. ment. Dis.*, **1952**, *30*: 480-492.

MAY & BAKER, LTD. Advance information. **1955**.

MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

RHEINBERGER, M. B. and JASPER, H. H. Electrical activity of the cerebral cortex in the unanesthetised cat. *Amer. J. Physiol.*, **1937**, *119*: 186-196.

TERZIAN, H. Electroencephalographic study of the central action of Largactil (4560 RP). *Rass. Neurol. veg.*, **1952**, *9*: 211.

VOGT, M. The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. *J. Physiol.*, **1954**, *123*: 451-481.

WASE, A. W., CHRISTENSEN, J. and POLLEY, E. The accumulation of S^{35}-chlorpromazine in brain. *Arch. Neurol. Psychiat.*, Chicago, **1956**, *75*: 54-56.

WIKLER, A. Pharmacologic dissociation of behaviour and EEG "sleep patterns" in dogs: morphine, N-allylnormorphine, and atropine. *Proc. Soc. exp. Biol. N.Y.*, **1952**, *79*: 261-265.

Reference: BRADLEY, P. B. and HANCE, A. J. The effect of chlorpromazine and methopromazine on the electrical activity of the brain in the cat. *EEG Clin. Neurophysiol.*, **1957**, *9*: 191-215.