STUDIES ON THE CARDIOVASCULAR ACTIONS OF CHLORPROMAZINE

III. EFFECTS ON CEREBRAL BLOOD FLOW, BLOOD PRESSURE, AND ELECTROCORTICOGRAM, AS RECORDED SIMULTANEOUSLY[1]

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ALTHOUGH CHLORPROMAZINE is primarily employed as a central nervous system depressant drug, Lehmann and Hanrahan (1) early reported convulsive seizures as a side-effect of therapy in psychiatric patients. Using the "cerveau isolé," Das, Dasgupta and Werner (2) also observed increased electrical activity following injections of the drug Indeed, in one case of chlorpromazine poisoning definite convulsions have been reported (3). Schlichther *et al* (4) have also more recently stated that as high as 52.4 per cent of the patients under intensive chlorpromazine therapy show convulsive seizures.

Preston (5), using cats, recorded both depression and stimulation of the central nervous system function, and suggested that "chlorpromazine is a neuronal stimulant and that the amygdala is particularly sensitive to this drug" Indeed, this author postulates that the "tranquillizing" effects of chlorpromazine might be due to the increased electrical activity of the amygdala.

Berger *et al* (6) have reported that in curarized cats artificially respired recordings of electrical changes from cortical and intercortical structures showed that "chlorpromazine at a dose of 1 to 15 mg /kg produced irregular slowing in the cerebral cortex, with outbursts of 7 to 10 cycles/sec of activity and occasionally slow waves of 2 to 3 cycles/sec." Margolis (7) has also concluded that in man "convulsions are far from uncommon in intensive chlorpromazine therapy."

On the contrary, Winkelman (8) observed that chlorpromazine potentiates the sedative actions of anti-convulsant drugs, and Goldman (9) could observe no evidence of seizures in 500 patients receiving up to 2 4 gm daily Kelly and Lawrence (10) have also reported that chlorpromazine decreases seizures in clinical and experimental tetanus, and Thibault (11) treated successfully a patient with severe postoperative convulsions with the so-called "lytic cocktail"

Lehmann has further postulated that the convulsions observed after chlorpromazine might be due to hypoxia of the brain following syncopal attacks due to orthostatic hypotension (12), but the problem has been somewhat obscured by the fact that in some patients it was noted that there had been a previous history of convulsive seizures (1).

In view of the above observations and in connection with other studies in this laboratory concerning the general cardiovascular actions of chlorpromazine (13, 14) it was of interest to investigate its influence upon the cerebral blood flow, blood pressure and associated electrocorticogram, as recorded simultaneously.

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In connection with these studies a number of similar experiments were also performed using diethazine (Diparcol). Jenkner and Lechner (16) have reported that the electrical abnormalities associated with cerebral trauma were normalized by administration of Diparcol. There are no other studies in the literature on this question so far as we are aware.

Methods

Dogs were used. In general, the animals were first etherized and artificial respiration instituted and maintained throughout all the experiments. The operative procedure consisted of a mid-line incision extending from the base of the nose to the occipital protuberance. The juncture of the sagittal and coronal sutures was exposed. Three small (4 mm. diameter) holes were trephined in the skull in such a manner as to form a triangular area, the middle of which was located approximately 1 cm. lateral and 1 cm. posterior, to the previously identified junction of the sutures. After this procedure was completed, the animals were curarized with succinylcholine (1 mg./cc.) by continuous intravenous drip, the total dose ranging from 200 mg. to 500 mg. The cerebral blood flow (C.B.F.) was measured by an indirect method, using the principle described by Ludwig (15) modified to record the temperature changes, after suitable calibration. A diagram of the electrical arrangement employed is shown in Figure 1. The

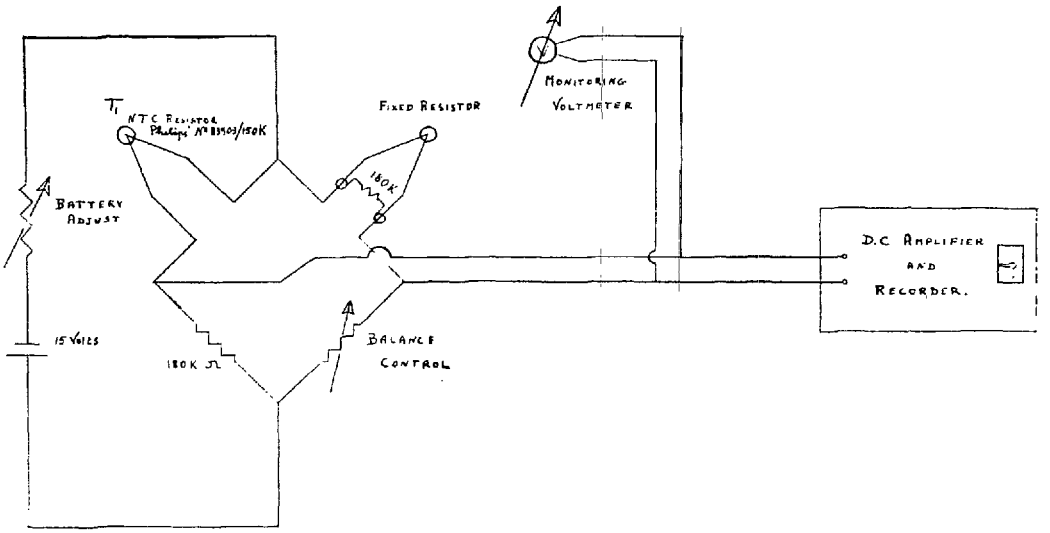


Figure 1. Diagram of bridge for measuring temperature variations due to changes in the cerebral blood flow (C.B.F.). The output of the bridge varies with the temperature at T_1, as recorded by the N.T.C. Resistor.

temperature changes of the underlying cerebral cortex are picked up by a N.T.C. Resistor.[3] The tip of the resistor (1 mm. in diameter) was placed through the middle orifice in the skull and directly in contact with the exposed cerebral cortex of the lateral gyrus on the left side. The electrocorticogram, referred to as E.E.G., was recorded from the same area of the brain by two fine platinum electrodes

[3]Negative Temperature Coefficient Resistor kindly supplied by the N. V. Phillips' Gleeinlampenfabrieken, Eindoven, Netherlands.

(0.5 mm. in diameter), inserted through the two orifices on either side of the resistor, approximately 1 cm. apart—the tip of the electrodes being placed on the unopened dura mater, in order to avoid unnecessary damage to the brain and excessive leakage of the cerebrospinal fluid.

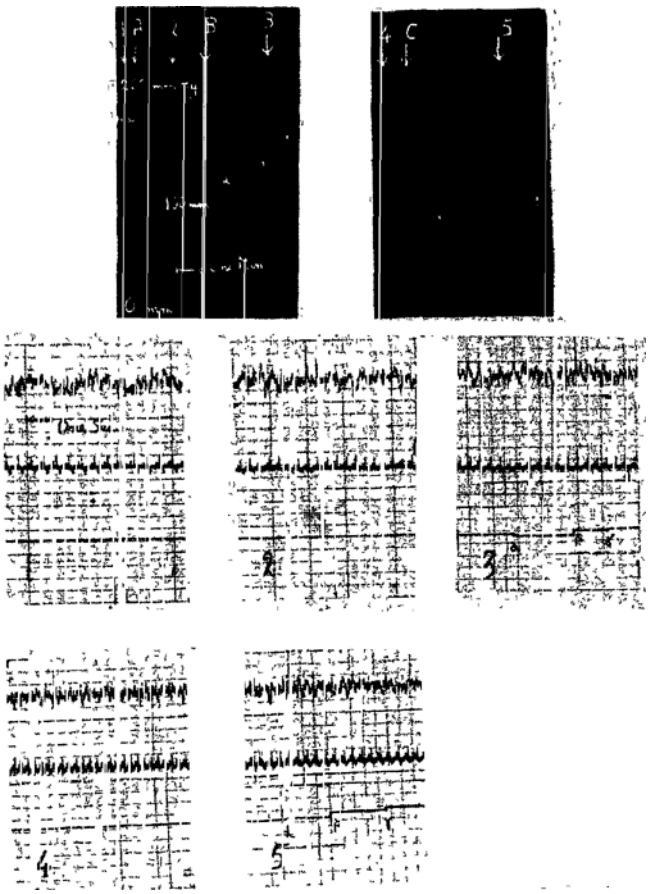


FIGURE 2. Dog, male, 14.0 kg. *Above*, kymographic blood pressure records—an interval of 10 minutes elapsed between each section, during which an additional dose of 10 mg./kg. of chlorpromazine was injected At A, chlorpromazine (5 mg./kg.) and at both B and C, chlorpromazine (10 mg./kg.) were injected. *Below*, sections of E.E.G., E.C.G. and C.B.F. records taken at nos. 1 to 5, as marked on the kymographic records—on nos. 3 and 5α, β and γ, corresponding to points so marked on the blood pressure record above.

Both the E.E.G. and C.B.F. changes were recorded continuously with a Sanborn Twin-Viso Cardiette.[4] The blood flow recording apparatus was calibrated so that 1°C. change in temperature produced an oscillation of 4 cm. on the recording paper. Electrocardiograms (Lead II) were recorded simultaneously on a sing e channel Viso-Cardiette (Sanborn) in most cases. The direct (femoral) blood pressure changes were also recorded kymographically. All animals were heparinized (1 mg./kg.), and all drugs were injected in an exposed femoral vein. Chlorpromazine hydrochloride (Largactil) in powder form[5] was used, and solutions freshly made up as needed.

[4]The writers are indebted to Dr. John Feeney of St. Mary's Hospital, Montreal, for the loan of this instrument.

[5]Kindly supplied by Poulenc Ltd, Montreal.

Results

Figures 2 and 3 demonstrate some examples of the changes which were observed following repeated administrations of large doses of chlorpromazine (5 to 20 mg /kg) Eight such experiments were performed

As can be seen in Figure 2 at A and B following injection of 5 and 10 mg /kg respectively, of chlorpromazine, there was a transient intense fall in blood pressure associated with some slight increase in heart rate Concomitantly, the cerebral blood flow (C B F) (nos 2 and 3) showed a slight decrease, while there appeared to be relatively little change on the E E G record During the interval between the two recordings a further dose of 10 mg /kg was given without much further change in the record, but a marked fall in blood pressure associated with an increase of the C B F Following a third similar dose of the drug (C) the C B F progressively increased as the fall in blood pressure persisted

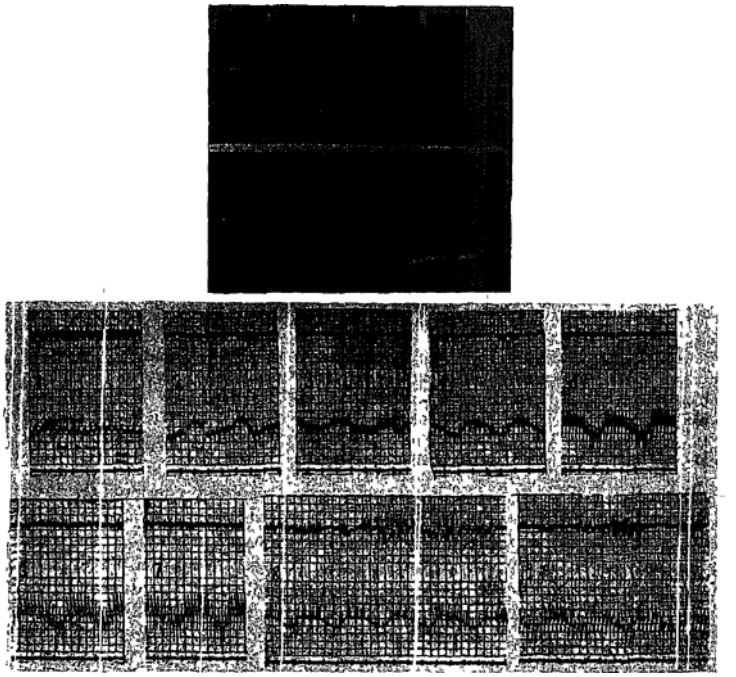


Figure 3 Dog, female, 8 6 kg (*a*) The upper and lower kymographic records are continuations, and sections of (*b*) the associated E E G (*above*) and E C G (*below*) records, taken at nos 1 to 9, as marked on the kymographic tracings, are shown At A, B and C, respectively, chlorpromazine (10 mg /kg) and at D, chlorpromazine (20 mg /kg) were injected

with no tendency to recovery The electrical activity at this point also showed some increase in both rate and voltage (nos 4 and 5)

Figure 3 shows again similar depressor responses following injections of chlorpromazine A, B, C and D, but the changes in electrical activity are more strikingly seen Thus with the prolonged hypotension there is a progressive increase in heart rate, the E E G showing at first a progressive slowing of electrical activity (nos 2 and 3), followed by an increase in fast electrical activity (nos 6 and 7), after the third dose of the drug (C), as compared to the pre-injection period (5) It is to be noted that when a larger dose (D) was given, periods of striking electrical outbursts developed (no 8) and continued intermittently thereafter (no 9)

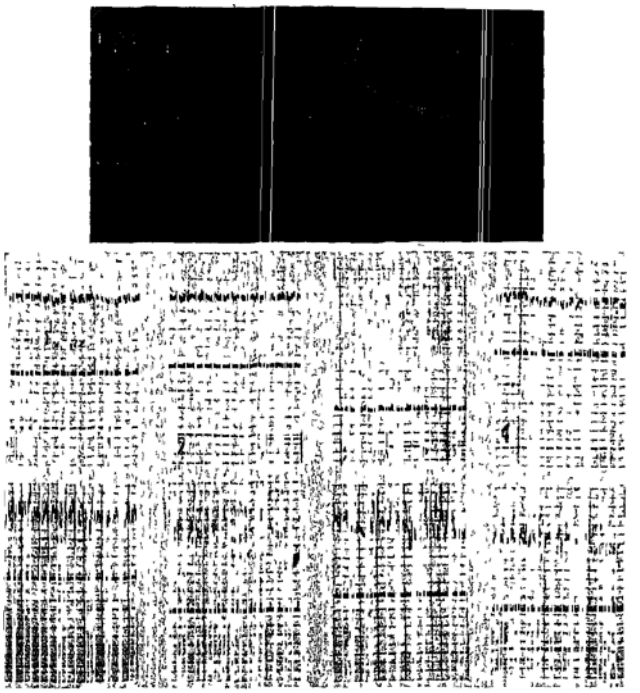


FIGURE 4 Dog, female, 7 4 kg Kymographic record of blood pressure *above* and sections of associated E E G , E C G and C B F records (*below*) taken at nos 1 to 8, as marked on the kymographic record, are shown The changes in C B F on nos 2, 3, 6 and 8, marked α, β and γ correspond to those shown on the blood pressure record At A and D, respectively, 10 mg /kg, and at B, 20 mg /kg of metrazol were injected At C, 10 mg /kg , and at E, 20 mg /kg , of chlorpromazine were given

From the above findings it is evident that with prolonged and repeated administrations of high doses of chlorpromazine definite localized electrical outbursts can be observed under these conditions On the other hand, as indicated in many of the initial responses, a single injection of the drug leads only to a decrease in cortical electrical activity

FIGURE 5 Dog, male, 12 0 kg Morphinized (10 mg /kg) before anaesthesia Kymographic record of the blood pressure (*above*) and sections of associated E E G , C B F , and E C G records (*below*) taken at Nos 1 to 7, as marked on the kymographic tracing, are shown. On nos 2, 3, 4, 5, 6, and 7 the changes correspond to the points marked by α, β and γ, on the record Between nos 5 and 6 the C B F recording stylus had to be adjusted (lowered) in order to permit recording, and start of record no 6 should therefore be considered as a direct continuation of the end of no 5 At A and E, metrazol (10 mg /kg), at B and D, chlorpromazine (10 mg /kg) and at C, adrenalin (100 μgm) were administered

In the second series of experiments it was of interest to investigate the influences of chlorpromazine upon the responses to various central nervous system stimulants including metrazol, picrotoxin, nikethamide and methamphetamine Some typical effects of the responses to metrazol are shown in Figures 4 and 5

Following control injections of metrazol (A and B), one sees a rise in blood pressure associated with a marked outburst of cortical stimulation (no 3) These effects were, however, accompanied by slowing of the heart and a considerable fall in the C B F The pre-injection conditions were soon restored (no 4), whereupon injection of chlorpromazine (C) rapidly induced marked tachycardia with increased E E G activity and there was a slight increase in C B F although there was a marked fall in blood pressure

A subsequent injection (D) of metrazol (one-half of the dose previously employed at B) now induced a more intense and sustained rise in blood pressure and stimulation in E E G activity There was, however, no associated bradycardia and a rise rather than a fall in C B F The excessive electrical activity persisted for the remainder of the experiment and appeared to be somewhat intensified (no 8) by the injection of a further large dose of chlorpromazine (E) Indeed, the E E G following chlorpromazine were now rather like those of metrazol, although the vascular changes were quite opposite Similar results were observed in 8 other similar experiments

Since it has been claimed that chlorpromazine can potentiate the central nervous system effects of analgesics, three similar experiments were performed on animals which were previously *morphinized* A typical example of the findings is shown in Figure 5 As can be seen, under those conditions, the initial injection of metrazol (A) produces a good rise in blood pressure associated with moderate E E G stimulation and a brief increase in C B F, which, however, returned to normal while the blood pressure was still maintained (no 2) However, following chlorpromazine injection at B there was now only a *moderate* depressor response, associated with tachycardia, and a sustained increase in C B.F, despite the fall in blood pressure (no 3)

Somewhat similar changes were observed following an injection of adrenalin at C, as shown in record no 4, and also following a repetition of the injection of chlorpromazine at D, as shown at no 5 Finally, repetition of the metrazol injection at E, although still inducing a pressor response, associated with the usual marked cortical stimulation (nos 6 and 7), there was an initial decrease followed by an increase in the rate of the C B F It is therefore clear that *chlorpromazine enhances the cortical stimulating action of metrazol, both in the non-morphinized and morphinized animal under these conditions*. However, although metrazol increases blood pressure and reduces C B F, chlorpromazine leads to a fall in blood pressure and a marked increase in the C B F It is also noteworthy that although chlorpromazine blocks the pressor response to injected adrenaline, the rise in blood pressure produced by metrazol still occurred However, in other experiments in non-morphinized animals, following a large dose (20 mg /kg) of chlorpromazine, the pressor response to metrazol was completely abolished although the cortical stimulation was still in evidence The observed pressor response to metrazol is therefore an adrenergic effect

Somewhat similar results were also obtained in similar experiments in which nikethamide (50 mg /kg) was employed instead of metrazol Under these conditions *the cortical stimulation following nikethamide is not abolished by chlorpromazine,* but the pressor response to the agent is reversed No observations were made on the C B F in this group of experiments

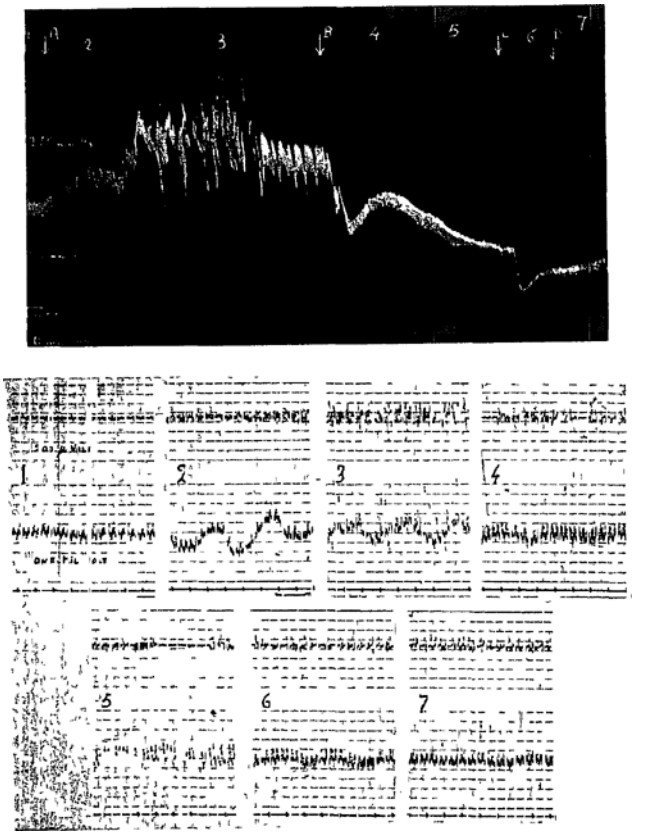


FIGURE 6 Dog, male, 9 5 kg Kymographic record of blood pressure (*above*) and sections of associated E E G and E C G records (*below*), taken at nos 1 to 7, as marked on the kymographic tracing, are shown At A, picrotoxin (2 mg /kg), at B and C, chlorpromazine (10 mg /kg), and at D, picrotoxin (1 mg /kg)

Figures 6 and 7 show typical examples of similar types of experiments in which the effects of chlorpromazine upon the responses to picrotoxin and methamphetamine were studied

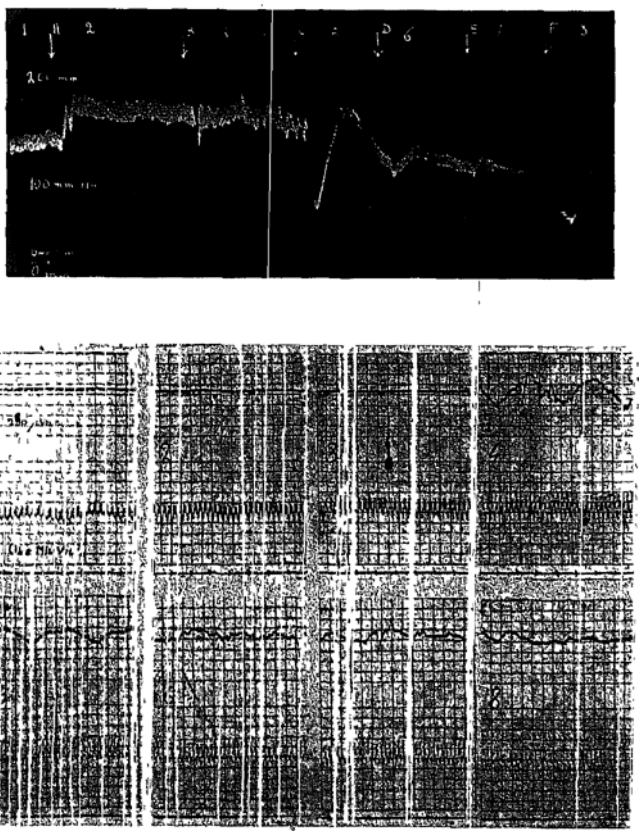
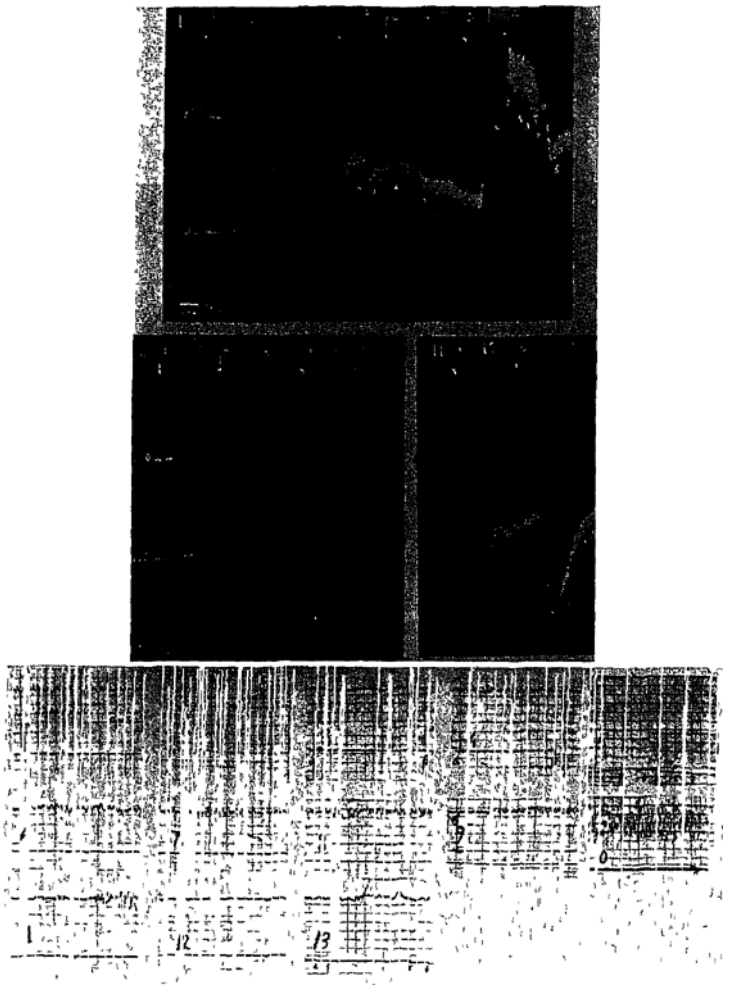
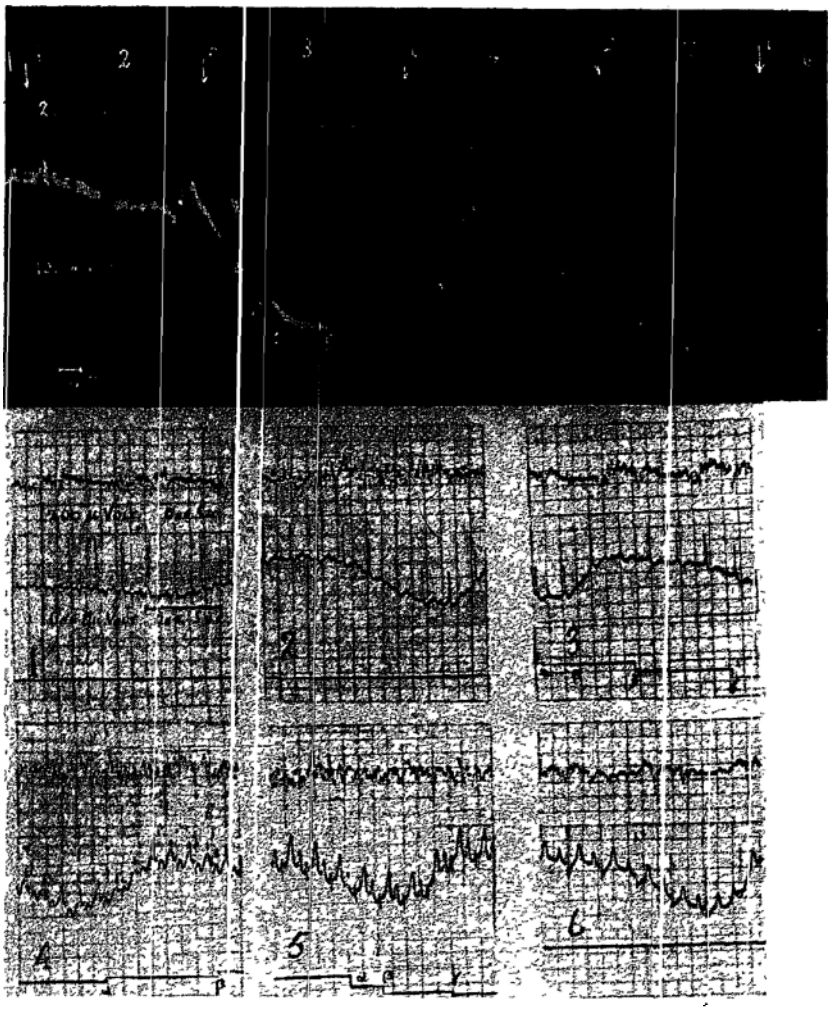


FIGURE 7 Dog, female, 14 2 kg Kymographic records of blood pressure and sections of associated E E G and E C G records taken at nos 1 to 8, as marked on the kymographic tracings, are shown At A and B, methamphetamine (1 and 2 mg /kg , respectively), at C, chlorpromazine (10 mg /kg), at D and E, metamphetamine (1 and 2 mg /kg , respectively), and at F. adrenalin (200 µgm) were injected



EXPERIMENT I

FIGURE 8 *Experiment I* Dog, male, 9 4 kg Kymographic record of blood pressure (*above*) and sections of associated E E C and C B F (*below*), taken at nos 1 to 13, as shown on the kymographic records On nos 3, 4, 5 and 13 the changes correspond to the points marked by α, β, γ and σ An interval of 18 minutes elapsed between the upper and the lower records and an interval of 16 minutes elapsed between the two lower sections At A, D, E, and H, metrazol (10 mg /kg), at B, C and F, ansolysen (0 7, 1 4 and 10 mg /kg , respectively), at C and J, chlorpromazine (10 mg /kg) and at I, adrenalin (100 μgm) were injected

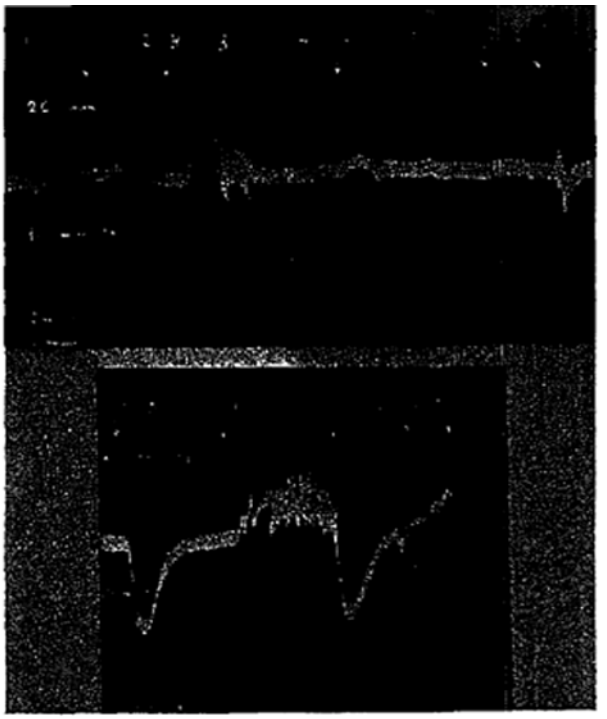


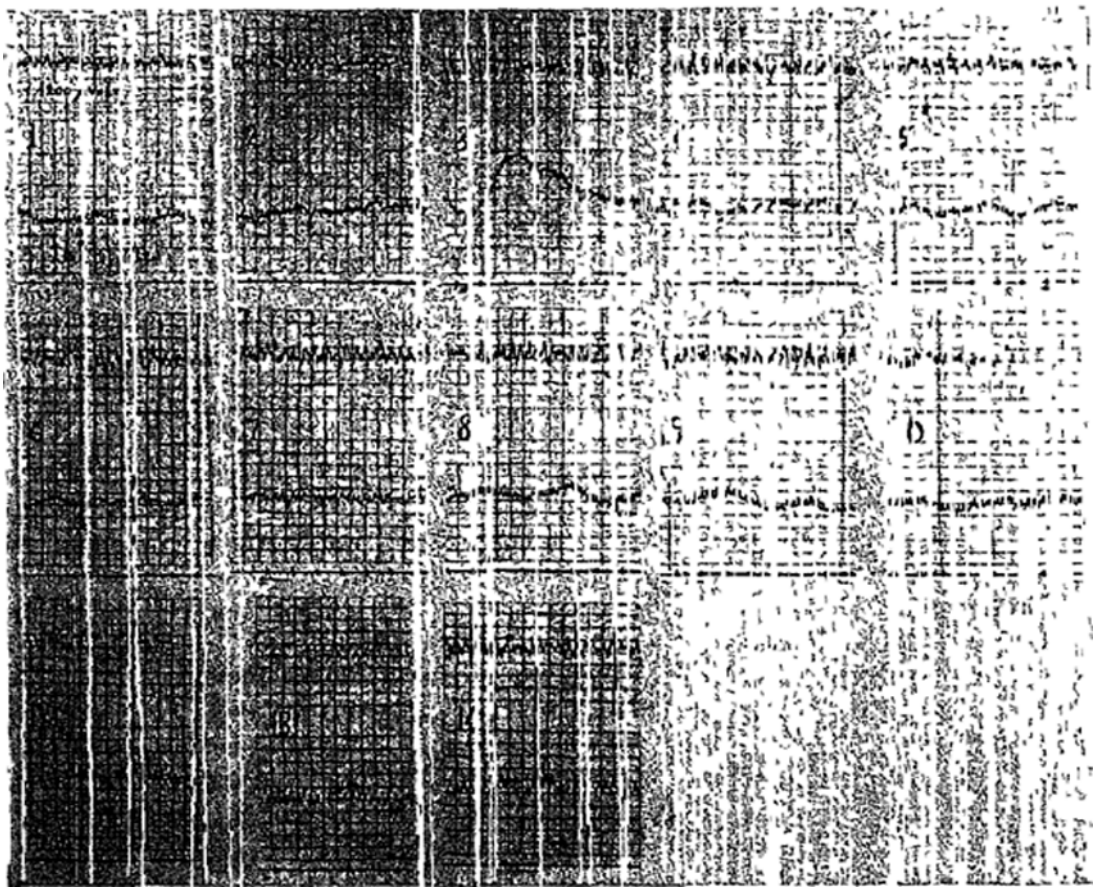
EXPERIMENT II

Experiment II. Dog, male, 8.2 kg. Record of blood pressure (*above*) and associated sections of E.E G., E.C.G. and C.B.F. records (*below*), taken at nos. 1 to 6, as marked on the kymographic tracing, are shown. On nos. 3, 4, and 5 the changes correspond again to the points marked by α, β, γ, and σ. At A and C, metrazol (10 mg /kg), at B, hexamethonium (5 mg./kg.) at D, chlorpromazine (10 mg /kg) and at E, adrenalin (200 μgm.) were injected.

As can be seen in Figure 6, following injection of picrotoxin (A), there is a progressive and sustained rise in blood pressure, associated with marked tachycardia and increased electrical activity of the cortex (nos. 2 and 3). Injections of chlorpromazine at B and C led to the usual depressor response with tachycardia, although the E.E.G. showed a curious alternation of high and low voltage waves (nos. 4 and 5), suggestive of excessive cortical stimulation and subsequent repetition of picrotoxin (D) produced no further changes in the E.E.G. The results suggest that *chlorpromazine does not prevent the cortical effects of picrotoxin.*

When methamphetamine was injected at A and B (Fig. 7), although there was a more sustained pressor response the E.E.G. showed only a slight initial stimulation followed by peculiar high voltage slow waves (no. 4). Following chlorpromazine (C) these waves still continued, although with reduced amplitude, but





on repeated injection of methamphetamine (D and E) slow high voltage waves again reappeared It is, therefore, clear that chlorpromazine *does not block the cortical effects of methamphetamine* It is of interest to note that although picrotoxin and methamphetamine are central nervous system stimulants, their effect on electrical activity as recorded is quite different (compare Figs 6 and 7)

Finally, some experiments were performed, in which chlorpromazine was injected following previous administration of (*a*) *ganglionic blockade*, induced either by injection of ansolyen or hexamethonium, or (*b*) *peripheral sympathetic blockade* induced by hydergin Some examples of the results obtained are shown in Figures 8 and 9

The most striking effects of the ganglionic blocking agents which were observed may be summarized as follows (*a*) There was no significant change in the pressor or E E G responses to metrazol (Fig 8, upper and lower sections), and (*b*) There was no sustained depressor response or evidence of stimulated cortical electrical activity following *repeated* injections of chlorpromazine

Following injection of the adrenergic blocking agent (hydergin) alone, both the E E G outbursts and the pressor responses to injected metrazol were, however, abolished (Fig 9, upper section), but subsequent *repeated* injections of chlorpromazine again led to neither the usual sustained depressor responses nor the increased cortical activity Curiously enough, when the responses to metrazol were tested after *both hydergin and chlorpromazine*, it is clear that both the usual E E G outbursts and the pressor responses were restored In addition, despite repeated chlorpromazine injections after hydergin the blood pressure was usually still well maintained and in some cases was higher at the end of the experiment than during the pre-injection control periods (see Fig 9, lower section) It would, therefore, appear that the hydergin-metrazol combination completely antagonizes the prolonged depressor effects of chlorpromazine, and associated with this action there was accentuation of the E E G outbursts induced by chlorpromazine This combination might, therefore, be of some antidotal value following excessive chlorpromazine administrations, and would appear to warrant further investigation in this connection

Some Observations on the Effects of Diethazine (Diparcol)

Diethazine is a close chemical relative of chlorpromazine, and it was therefore of some interest to compare its effects with those of chlorpromazine under the conditions of these experiments

In Figures 10 and 11 are illustrated some of the typical responses observed after repeated diethazine injections, and the influence of this agent upon the responses to metrazol As is evident from Figure 10, the depressor responses to diethazine were much less sustained than those observed after chlorpromazine

Figure 9 Dog, female, 7 5 kg (*a*) The upper and lower kymographic records are continuous and associated sections of (*b*) the E.E G and E C G taken at nos 1 to 14, as marked on the kymographic tracings, are shown At A, B, D, G and I, 5 mg , 15 mg , 10 mg , 20 mg , and 10 mg /kg , respectively, of metrazol were injected Hydergin (0 3 mg /kg) was given at C and J, and chlorpromazine (10 mg /kg) at F and H

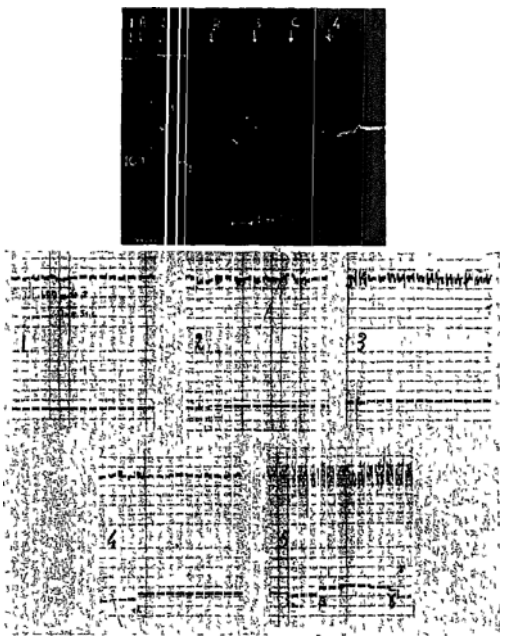


FIGURE 10 Dog, male, 17 0 kg Kymographic record of blood pressure (*above*) and sections of associated E E G, and E C G and C B F (*below*), taken at nos 1 to 4, as marked on the kymographic tracing, are shown On No 2 the changes recorded correspond to the points marked by α, β and γ At A (5 mg), and at B and C (10 mg /kg) diethazine were injected

These effects were also associated with more intense cortical stimulation and increased cerebral blood flow (nos 3 and 4) In addition, both the central stimulation (E E G outbursts) and the pressor responses following metrazol, appeared to be potentiated by diethazine, with concomitant augmented cerebral blood flow (Fig 11) However, following sympathetic blockade with hydergin, all of these effects are antagonized Thus, as can be seen from the records, both the usual pressor effect and cortical stimulation following metrazol are blocked However, with superimposed diethazine in such experiments, these responses to metrazol are again restored

It is also noteworthy that after injection of hydergin alone, the cerebral blood flow is decreased, despite the rise in blood pressure (Fig 12, no 4) and subsequent injections of metrazol or diethazine did not significantly restore the cerebral blood flow to normal although blood pressure again was well main-

tained From the above findings, it is clear that the over-all effects of diethazine were rather similar to those of chlorpromazine, except that they were less sustained

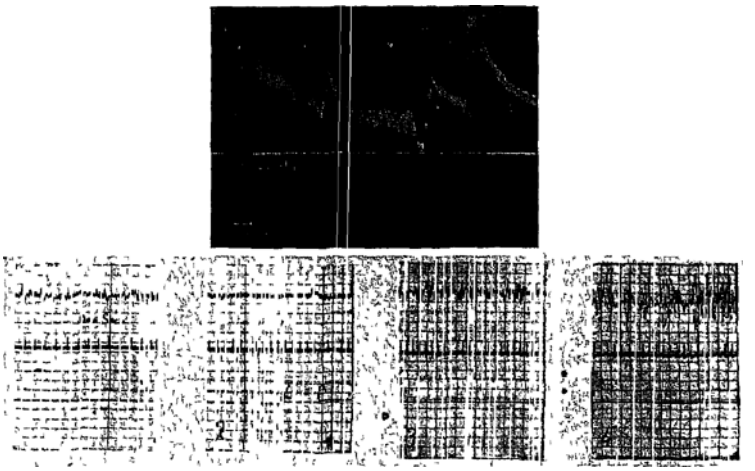


FIGURE 11 Dog, male, 9 6 kg Kymographic record of blood pressure (*above*) and sections of associated E E G and C B F records (*below*), taken at nos 1 to 5, as marked on the kymographic tracing, are shown On nos 4 and 5 the changes recorded correspond to the points marked by α, β and γ At A, B and D, metrazol (10 mg /kg), and at C, diethazine (5 mg /kg) were injected

SUMMARY AND CONCLUSIONS

In curarized dogs under artificial respiration, it was observed that (*a*) chlorpromazine in high and repeated doses (5 to 20 mg /kg) can induce marked fall in blood pressure, tachycardia, and increased cerebral blood flow, (*b*) previous injections of similar high doses of chlorpromazine do not abolish either the pressor responses or cortical stimulation (outbursts) induced by metrazol, and both agents appear rather to lead to enhanced cortical outbursts, (*c*) chlorpromazine also does not affect the cortical stimulation (E E G changes) following injections of nikethamide, picrotoxin, or amphetamine, *but antagonizes the blood pressure responses to these agents*, (*d*) after ganglionic-blockade (ansolysen or hexamethonium) cortical changes induced by chlorpromazine are not prevented, but its depressor response is lessened by ansolysen, but on the contrary enhanced by hexamethonium, (*e*) after sympathetic blockade (hydergin) both the central stimulation and pressor responses to metrazol are prevented, but the depressor response to chlorpromazine is antagonized and combined hydergin-metrazol treatment appears to prevent the usually observed depressor effects of

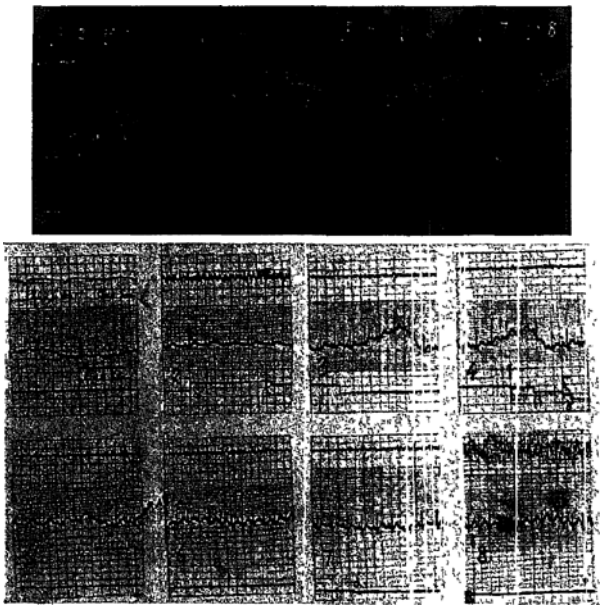


FIGURE 12 Dog, male, 7 4 kg Kymographic record of blood pressure (*above*), and sections of associated E E G, E C G, and C B F records (*below*), taken at nos 1 to 8, as marked on the kymographic tracing, are shown On nos 2, 4 and 7 the changes recorded correspond to the points marked α, β and γ At A, D, E and G, metrazol (10 mg /kg) at B, diethazine (5 mg /kg), at C, hydergin (1 mg /kg) and at F, diethazine (5 mg /kg) were injected

excessive chlorpromazine injections, and (*f*) diethazine appears to exert similar actions to those of chlorpromazine, but its effects are less sustained

RÉSUMÉ

Chez des chiens curarisés placés sous respiration artificielle, on a observé certaines réactions à savoir que (*a*) la chlorpromazine à hautes doses répétées (5 à 20 mg /kg) peut produire une chute marquée de la pression sanguine, une tachycardie et une augmentation de l'afflux sanguin au niveau du cerveau, (*b*) les injections antérieures de telles doses elevées de chlorpromazine n'abolissent ni l'effect sur la pression ni la stimulation du cortex causés par le metrazol, les deux agents semblent plutôt produire des réactions électriques soudaines et violentes dans le cortex, (*c*) la chlorpromazine n'affecte pas la stimulation corticale, à la suite d'injections soit de coramine ou de picrotoxine ou de amphetamine, mais empêche les réponses de la pression sanguine à ces agents, (*d*) après un blocage

ganglionnaire (ansolysen ou hexamethonium) on ne prévient pas les changements corticaux apportés par la chlorpromazine, et l'effet depresseur est diminué par l'ansolysen alors qu'il est augmenté par l'hexamethonium, (*e*) après un blocage sympathique (hydergine) la stimulation centrale et l'effet sur la pression causés par le metrazol sont nuls L'effet dépresseur de la chlorpromazine sur la circulation sanguine est inversé et le traitement à l'hydergine associé au metrazol semble prévenir cet effet dépresseur habituellement observé à la suite des injections de doses excessives de chlorpromazine, et qu'enfin, la diethazine semble produire les mêmes réactions que la chlorpromazine mais avec des effets qui sont moins soutenus

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