THE PHARMACODYNAMICAL ACTION OF CHLORALOSE.

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Introduction. Chloralose was introduced some years ago by Richet for experiments on animals. The drug does not appear to have been very extensively used as an anæsthetic for such experiments, although, as we shall show, it possesses several obvious advantages. The chloralose used in our experiments was obtained from Messrs Baird and Tatlock, Ltd., its origin being French. We have been informed that it is prepared by heating an anhydrous mixture of chloral and glucose at 100° C. for about one hour. The residue is treated with a little water and then boiling ether; the toxic isomer, parachloralose is eliminated by crystallisation. The formula is $C_8H_{11}O_6Cl_3$.

A solution saturated at 40° C. was made and injected intravenously.

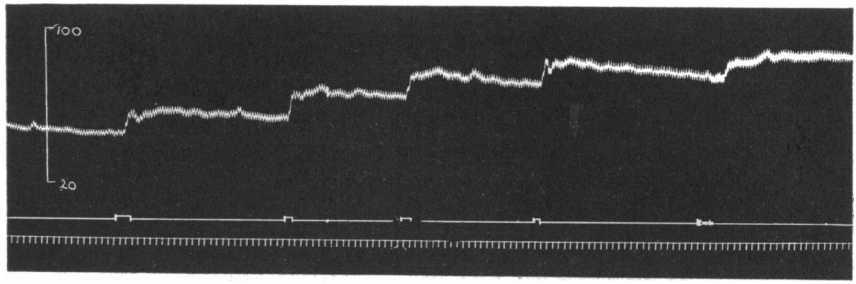
All the experiments have been performed upon decerebrate cats, after all the ether has been expired.

Action on the mean arterial blood-pressure. 10 c.c. of the above solution injected intravenously is sufficient to raise the blood-pressure approximately 20 mm. of Hg. The effect is not observed immediately, but follows upon the initial rise caused by the saline. The blood-pressure remains raised to its new level for a considerable time, and by means of repeated injections can be stepped up to more than twice the original height (Fig. 1).

Control experiments have been carried out with glucose solution, and with chloral preparations, and since under certain conditions normal saline solution will produce considerable rises of pressure, we have performed numerous controls with this solution also. All of these have failed to produce the results obtained with chloralose. It is significant that intact animals anæsthetised with chloralose always have a high initial blood-pressure.

Action on the somatic nerves. Stimulation of the sciatic and anterior crural nerves with the strongest available stimuli failed to elicit any

reflex responses when the animal was under chloralose. Weak stimuli were equally ineffective. This inhibitory action of chloralose is manifested quickly and can be shown five minutes after the first injection.



Time tracings indicate periods of 5 seconds.

Fig. 1. Cat: decerebrate. Intravenous injections of 10 c.c. of chloralose solution (sat. 40° C.) resulting in raising the mean blood-pressure from 40 mm. Hg to 90 mm. Hg Note the "stepping up" effect.

Action on depressor reflexes. Vaso-motor reflexes of a depressor character obtained by scratching the skin, or kneading the muscles or intestine are considerably augmented after administration of chloralose. This is particularly marked in the case of the intestine; indeed, the increased sensitivity of the vaso-motor response is so great that falls of blood-pressure occur when the gut is kneaded intra-abdominally before

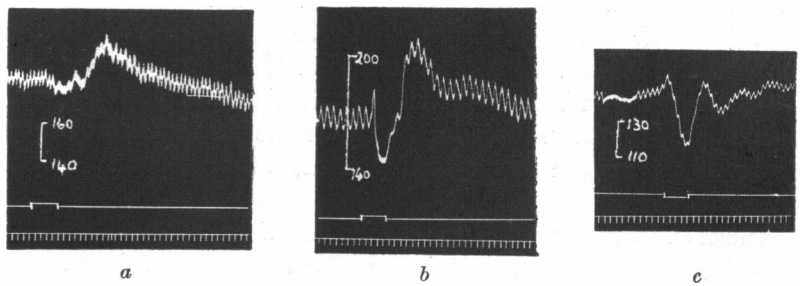


Fig. 2. Cat: decerebrate. (*a*) Intra-abdominal kneading of intestine showing initial mechanical rise followed by a marked secondary rise due to autacoid pressor substance. (*b*) 10 c.c. chloralose (sat. 40° C.) administered intravenously 5 minutes before stimulation. Initial vaso-motor fall although kneading of intestine is intra-abdominal. Secondary rise still present. (*c*) 15 min. later, vaso-motor fall alone remaining.

the normal pressor effect due to the autacoid substance (Vincent and Thompson (1)) (Fig. 2). The hypersensitivity of nerve terminals, especially

those concerned in reflex dilatation of the pupil, has been observed by McDowall(2) under chloralose anæsthesia in intact animals.

Action on the splanchnic nerve. Stimulation of the peripheral end of the divided left splanchnic nerve in the abdomen after an injection of chloralose results in a remarkable exaggeration of the whole curve of blood-pressure. It becomes noticeable 5 minutes after injection, and reaches its maximum 25 minutes later. Repeated injections still further increase the rise, so that eventually rises nine or ten times the height of the original rise are obtained with the same strength of stimulus (Figs. 3*a* and 3*b*). We have observed that the increase in height of the

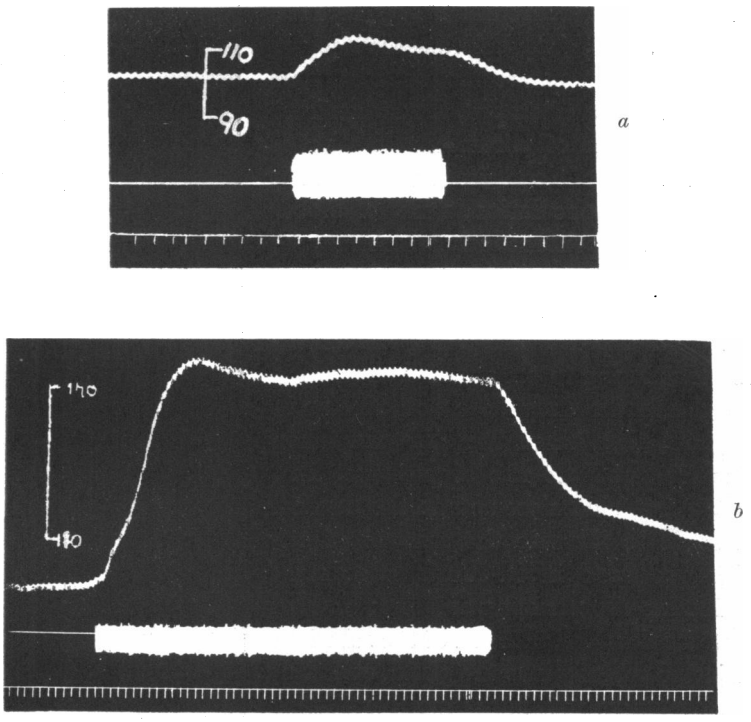


Fig. 3*a*. Cat: decerebrate. Stimulation of left splanchnic nerve before injection of chloralose.

Fig. 3*b*. Stimulation of left splanchnic nerve with same strength of current 1 hour after two intravenous injections of 10 c.c. chloralose solution (sat. 40° C.).

curve is greater at the end of half an hour if the nerve is stimulated at intervals of about 5 minutes than if it is left undisturbed during this period.

Division of both vagi in the neck made no difference to the results, and thus a parasympathetic action may be excluded.

Interaction of the adrenal glands. If the adrenaline veins are clamped, and while the clips are in position the left splanchnic nerve is stimulated, whether chloralose was given before or after putting them on, the effect on blood-pressure is no greater than it is without chloralose. Clearly the presence of the drug in the vessels on which the splanchnic acts does not by itself bring about any increase of the effect. But if the chloralose is injected and allowed to circulate for a short time before the veins are clamped, then when later the clips are taken off a remarkable effect is observed. As the blood from the gland is released into the circulation, a rise of blood-pressure occurs spontaneously which may be very large if the amount of chloralose given was large (Fig. 5). If, on the other hand, the veins were clamped before giving the chloralose, so that owing to the arrested circulation in the glands the drug does not effectively reach them, then when the clips are taken off there is but little rise of pressure. This suggested that chloralose acts in the adrenal gland so as to increase the amount of adrenaline produced in it. And accordingly the following experiment was done: a small amount of chloralose, 0·25 c.c. of the solution, was injected directly into the gland, and then after extirpation of both the semi-lunar ganglia, the post-ganglionic fibres to the gland were stimulated, and the effect shown in Fig. 6 was obtained, a considerable rise of blood-pressure.

It is true the sudden descent of the tracing when the stimulation stopped is difficult to account for, but the result, taken together

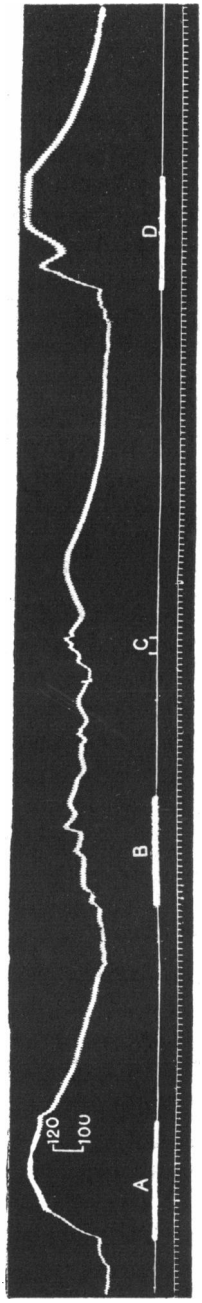


Fig. 4. Cat: decerebrate. 10 c.c. chloralose (sat. 40° C.) 30 min. previously. (*A*) Stimulation of left splanchnic nerve with adrenal veins open; (*B*) with veins clamped; (*C*) removal of clamps followed by rise, (*D*) stimulation with veins open. Same strength of stimulation used for (*A*), (*B*) and (*D*).

with the effect of releasing the blood from the glands when chloralose was given before obstructing the circulation, is in favour of an increased formation of adrenaline under the influence of the drug.

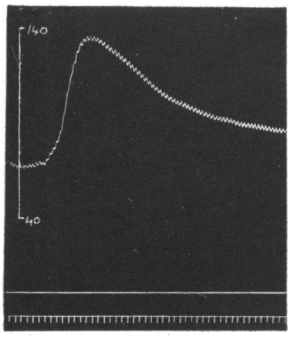


Fig. 5

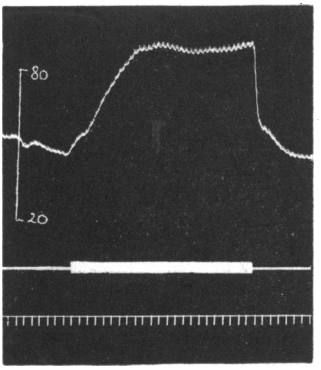


Fig. 6

Fig. 5. Cat: decerebrate. 10 c.c. chloralose (sat. 40° C.). 20 min. previously. Large rise of blood-pressure consequent upon release of clips on adrenal veins after four stimulations of left splanchnic nerve with veins clamped.

Fig. 6. Cat: decerebrate. Semi-lunar ganglia removed. 0·25 c.c. chloralose (sat. 40° C.) injected directly into the left adrenal gland. Stimulation of fibres from semi-lunar ganglia to the gland. (Prior to injection only very slight rises could be obtained.)

Injection of adrenaline. When a mixture of chloralose solution (saturated at 40° C.) and adrenaline solutions of various strengths is intravenously injected, a large and long-sustained rise of blood-pressure is caused instead of the ordinary transitory rise obtained by injection of adrenaline alone. The persistence of the rise is remarkable, and when doses of 0·1 mg. of adrenaline are given, the maximum height may be maintained for longer than ten minutes (Fig. 7).

A similar result is effected when adrenaline is administered to an intact or decerebrate animal under chloralose.

If adrenaline be injected intravenously whilst this sustained rise is in progress, falls of blood-pressure occur (Fig. 8). It appears to be impossible to produce a pressor response by means of adrenaline when this rise is present. Even large doses of adrenaline—2 or 3 mg.—result in falls.

Discussion of Results.

The experiments relating to clamping the adrenal veins clearly demonstrate that chloralose activates the secretion of adrenaline. Precisely how this is done is not obvious, but it appears to be an action

on a local mechanism consisting of the gland itself and possibly the nerve-fibres reaching it from the semi-lunar ganglia, as evidenced by the large

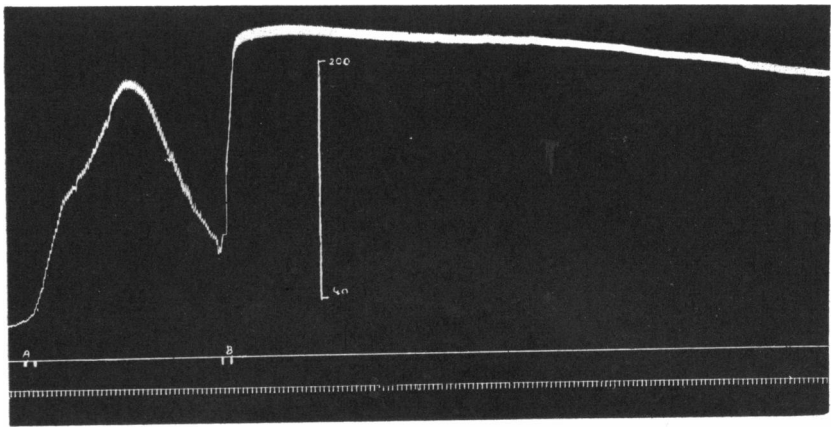


Fig. 7. Cat: decerebrate. (*a*) Injection of 0·1 mg. adrenaline. (*b*) Injection of 0·1 mg. adrenaline and 10 c.c. of chloralose (sat. 40° C.). (The pressure was maintained at a high level for 10 minutes longer than shown in the above figure.)

rise of blood-pressure elicited from stimulation of the post-ganglionic fibres to the gland after chloralose has been injected into it and the ganglia removed.

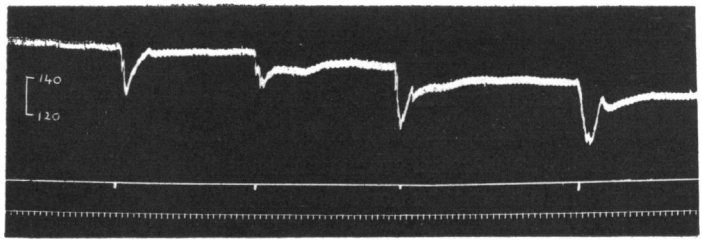


Fig. 8. Cat: decerebrate. Sustained rise of blood-pressure produced by injection of adrenaline plus chloralose. Injection of adrenaline of various strengths: (*a*) 0·01 mg.; (*b*) 0·2 mg.; (*c*) 0·01 mg.; (*d*) 0·005 mg.—during the rise caused falls of blood-pressure.

This explains the increase in the size of the splanchnic curve, the diminution after clamping the adrenal veins confirming such an explanation. Now it is found that the rise of blood-pressure produced by stimulation of the left splanchnic nerve 30 minutes after injection of chloralose

is greater if stimulation be applied to the nerve during this interval. This seems to indicate that the ultimate products of each stimulation sensitise the secretory mechanism in the gland for the next stimulation. It may be a direct effect upon the nerve terminations, or a catalytic action upon the precursor of adrenaline produced by stimulation of the nerve fibres.

In support of this theory is the fact that adrenaline is stabilised by chloralose, as shown by the long sustained rises. Hence the permanent raising of the mean blood-pressure. Possibly a weak chemical compound is formed between chloralose and adrenaline, which is more stable than adrenaline. This compound sensitises the nerve terminals. We think that this is the interpretation of the hypersensitivity of the nerve terminals in other parts of the body, and it is significant that the effect is most marked at sympathetic terminals.

Summary.

Experiments have been performed upon decerebrate cats under the influence of chloralose to demonstrate the action of the anæsthetic upon the mean blood-pressure, the somatic, nerves, nerve terminals, and the left splanchnic nerve, and to show the effects of injection of adrenaline.

Reasons are advanced for the belief that chloralose stimulates the production and discharge of adrenaline from the adrenal gland. We have also given evidence for the stabilisation of adrenaline in the body, as, for example, that injected into the blood, by the formation of a stable compound. This compound sensitises nerve terminals and tends to raise permanently the mean blood-pressure.

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REFERENCES.

1. Vincent and Thompson. This Journ. 65. 327. 1928.
2. McDowall. Quart. Journ. Exper. Physiol. 15. 178. 1925.