THE PHYSIOLOGICAL ACTION OF THE ALKALOIDS DERIVED FROM ANHALONIUM LEWINII.

By WALTER E. DIXON, M.D., B.Sc. Lond., *Salters' Company Research Fellow at St Thomas's Hospital.* (Eight Figures in Text.)

ANHALONIUM LEWINII, so called from its discoverer, Lewin, who in 1888 first directed attention to it[1], belongs to the small group of Melocacteæ, and is native to Mexico. It makes the seventh known variety of the Anhalonia, but besides some discussion which has occurred with regard to the botanical position it should occupy, it has attracted but little attention from investigators, probably largely on account of the difficulty in obtaining specimens. The genus Anhalonium is easily distinguished from Echinocactus and Mamillaria in being quite free from spines[2].

A. Lewinii is a small cactus, having roughly the shape and size of a radish. It is spoken of familiarly by traders in Mexico as "Mescal," and is occasionally confounded with another Mescal in Arizona, the "Agave," from which the Apaches prepared an intoxicating drink[3].

It has long been known that the Kiowa and other Mexican Indians ate some substance in their religious ceremonies which was stated to possess remarkable physiological properties[4], but in proportion as it was held sacred by the Indians it was condemned by the early missionaries and its exportation was prohibited.

The plant first attracted attention on account of its vision-producing properties, which all observers agree it possesses, and most of the literature on the subject which has already appeared consists principally in detailed accounts of these phenomena.

[1] *Arch. f. exp. Path. and Pharm.* XXIV. p. 401; XXXIV. pp. 65 and 374. *Therap. Gaz.* 1888, p. 235.

[2] *Report Missouri Botanic Gardens*, 1898, p. 127.

[3] Henning. *Therap. Gaz.* 1888, p. 232.

[4] Prentiss and Morgan. *Op. cit.* 1896, p. 7.

Lewin, in his original paper, besides describing the morphology of the plant, tried the effect of a watery extract on frogs, pigeons, and rabbits, and mentions convulsions comparable to those of strychnine as occurring in each case: he also described an alkaloid, "anhalonnine," which he regarded as the active constituent, but which in reality was a mixture of several alkaloids.

Prentiss and Morgan[1], after eating the "buttons," state that with smaller doses the pupils became dilated, muscular depression and inability to sleep assert themselves, and later colour visions occur, but these only with closed eyes. After larger doses (4—8 buttons) there are fine tremors, loss of conception of time, blunting of sensation and sense of smell.

Weir Mitchell[2] used both an extract and tincture of the buttons, taking three of the latter for a full dose. He describes a stage of exhilaration and talkativeness, in which there is dilation of pupils, flushing of the face, and rather rapid pulse, followed by a condition which he describes as one of "deliciously languid ease and elated sense of superiority." Later, colour visions are seen, both with the eyes closed and open, and a sleeplessness, not accompanied however by any uneasy or restless feelings. The visions which Weir Mitchell lays great stress upon, and describes with much detail, cannot be accepted as the average effect, considering that he admits himself to be a good subject for visions, and that during the few days after taking the drug was able to conjure up identical visions, although with some loss of definition.

Eshner, in the same paper as above, states that it caused in him a condition of "muscular insensibility," or "motor anæsthesia."

Havelock Ellis[3], after taking an infusion of three buttons, mentions a first stage of exhilaration, which, however, quickly passed off, giving rise to a condition of heightened muscular irritability, faintness, difficulty in concentrating attention, singing in the ears, vague sense of perfume in the air, and the colour visions. These latter consisted of intensely coloured sensations moving to and fro, and producing the impression of constant flickering, and were at first only seen with closed eyes. All objects presented a heightened colour, and vague shadows floated before the eyes, giving the room rather the appearance of a picture than an actual reality.

[1] Prentiss and Morgan. *Op. cit.* 1896, p. 4.
[2] Weir Mitchell. *Brit. Med. Journ.* Dec. 1896.
[3] Ellis. *Lancet*, I. 97, p. 1540.

Heffter[1] described a method by means of which four alkaloids could be extracted from the plant. He treated the powdered buttons with 70% alcohol, filtered, and rendered the filtrate alkaline with ammonia, then:

			M.P.
Chloroform removed	mezcaline	$C_{11}H_{17}NO_3$	151
Ether „	anhalonidine	$C_{12}H_{15}NO_3$	150–154
	anhalonnine	$C_{12}H_{15}NO_3$	855
	lophophorine	$C_{13}H_{17}NO_3$	(amorphous)

Edmund White, Pharmaceutist at St Thomas's Hospital, in a private communication to myself has amplified Heffter's work, and prepared the alkaloids in the following proportions from the crude "buttons":

1. Mezcaline 2. Anhalonidine	1·16 per cent.	(about equal amounts of each)
3. Anhalonnine	·46 „	
4. Lophophorine	·14 „	

These alkaloids were supplied to me by Mr White in a beautifully crystalline condition, except Lophophorine, which appears to be only crystalline in the form of a salt. All were freely soluble in distilled water, alcohol, or normal saline, and possessed remarkable similarity in their physiological actions.

Anhalonnine and anhalonidine have the same formula, and are isomeric; their physiological effects are identical. Lophophorine belongs to the same series, differing only by the addition of CH_2: this, however, appears to have the effect of increasing the toxicity. Mezcaline, though apparently differing somewhat in constitution, is also closely allied, and its physiological action is almost indistinguishable from that of anhalonnine.

The animals used in these experiments have been principally dogs and cats, but investigations have also been made on herbivorous animals, and as far as practicable on the human subject.

The alkaloids were invariably used in the form of a 1% solution in normal saline, the method of administration being generally subcutaneous injection, although intraperitoneal injection and administration by the mouth were also used on occasion.

Action upon the skin. A 5% solution applied directly to the conjunctiva produces no noticeable effect: also subcutaneous and intra-

[1] Heffter. *Berichte*, I. pp. 221—229. 1896.

peritoneal injections are not accompanied by any local irritation. In the human subject there is no sensible increase of the perspiration.

Mouth. In all cases there is an increased flow of saliva, which becomes equally manifest whether the alkaloid is administered by the mouth or subcutaneously. In the case of cats after the injection of ·1 gramme of anhalonnine, salivation goes on for two or three hours; about 1 c.c. of this saliva injected into a frog shows the typical effect of the alkaloid.

Gastro-intestinal Canal. After even very large doses of the alkaloid, it is not common to get vomiting, although this does occur occasionally. The emetic effects described by the Americans who ate the crude buttons may to some extent have been due to the cushion of fine hairs situated on the top of the dried plant.

Small doses (*i.e.* all doses administered to man in therapeutic quantity) produce constipation, but when the dose is very large diarrhœa may be produced, and even in some cases bloody stools. In one experiment on a cat, the hypodermic injection of ·08 gramme was followed in less than one hour by defæcation, and later by the passage of a quantity of mucoid blood-stained material. Post mortem, this animal showed marked congestion of the last six inches of the rectum, the rest of the intestinal tract being normal. This action is interesting as producing its results indirectly through the nervous system.

Blood. No effect is produced on the blood, which was examined in animals which had died after the administration of a large dose of the alkaloid, and also by treating fresh blood outside the body.

Circulatory System. One of the most characteristic effects of these alkaloids is their action on the heart and circulatory system, and this is the more remarkable in that some American observers have denied such action. A few drops of a 1 % solution of the alkaloid in normal saline applied directly to the frog's heart produces a marked effect, the rapidity of the beat being diminished, but the duration being increased; for example, in one case where the heart was beating normally at 31 to the minute, after painting with the solution the result was as follows:

After	5	mins.	23	beats a minute.	Beating with increased force.
„	10	„	19	„ „	
„	15	„	16	„ „	
„	20	„	14	„ „	Beating with greatly diminished force.
„	60	„	8	„ „	

The heart subsequently stopped, though the sinus continued beating after the auricles and ventricles had ceased.

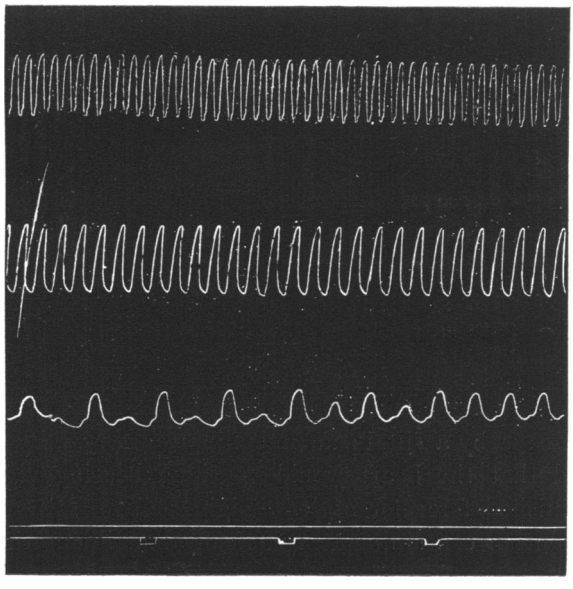

Fig. 1. Shows the effect of applying anhalonnine (1 % in Ringer) to the frog's heart. Tracing I. is normal; II. effect one minute after application; III. fifteen minutes after. Time represents 20 secs.

Control experiments were performed, using normal saline, but without causing alteration in the rhythm.

Perfusion experiments were performed with the frog's heart after

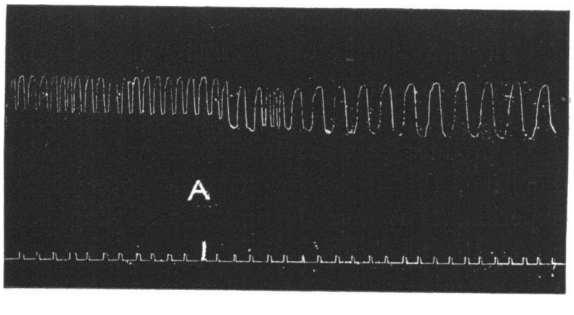

Fig. 2. Immediate effect of applying (1 % in Ringer's solution) to the frog's heart. The point *A* represents the moment of application.

the method of Brodie. A cannula having been tied in one of the hepatic veins, Ringer's fluid was slowly forced through the heart and

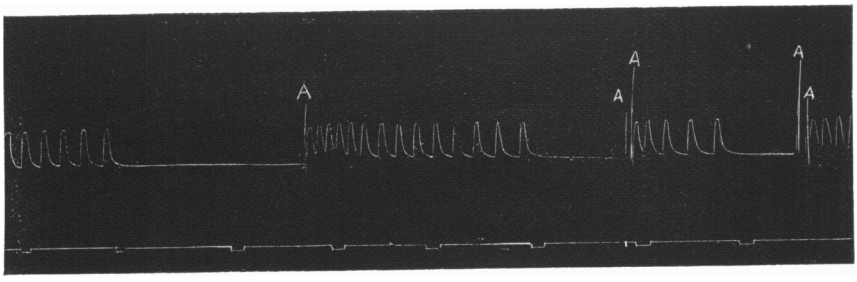

Fig. 3. Perfusion of the frog's heart after the method of Brodie. The figure represents the condition of affairs five minutes after a ·25 % solution of anhalonnine in Ringer had been substituted for ordinary Ringer's solution. *A* represents the moment at which mechanical stimulation was applied. Time = 20 secs.

allowed to escape by a slit in an innominate artery. By this method it was found that the heart would continue beating vigorously and with undiminished force for at least eight hours. If now at a given moment a solution containing 1 in 1000 of alkaloid in Ringer be substituted for Ringer, the effect is characteristic: slowing immediately occurs, and after a few minutes the heart suddenly ceases to beat in diastole; artificial stimulation, such as pricking, is sufficient to start it again, only however to stop once more, the stoppages occurring quicker after each repetition (Figs. 1 and 3). Stimulation of the vagus now shows that it is completely paralysed. Stimulation of the crescent will for a time produce quickening of the heart after the vagus ceases to inhibit, but this effect also is soon lost.

If a few drops of a half per cent. atropine solution are applied to a frog's heart which has been previously slowed by mezcaline, no alteration in the rhythm occurs; this is interesting as being in marked contrast to the slowing produced by muscarine.

If a frog's heart, to which a ·1 % solution of nicotine has been applied, so as to produce paralysis of the nerve cells, be treated by a mezcaline solution, the typical slowing is immediately produced. From these experiments it appears that the slowing is produced by the direct action of the alkaloid on cardiac muscle fibre.

In mammalia its effects are also characteristic; a small injection (·01 gramme mezcaline) into the jugular vein of a cat at first lowers the blood-pressure for a few seconds, but soon a considerable and per-

manent rise occurs; with this alteration in pressure there is cardiac slowing, which however passes off in a few minutes, the heart resuming its normal rhythm (Figs. 4 and 5).

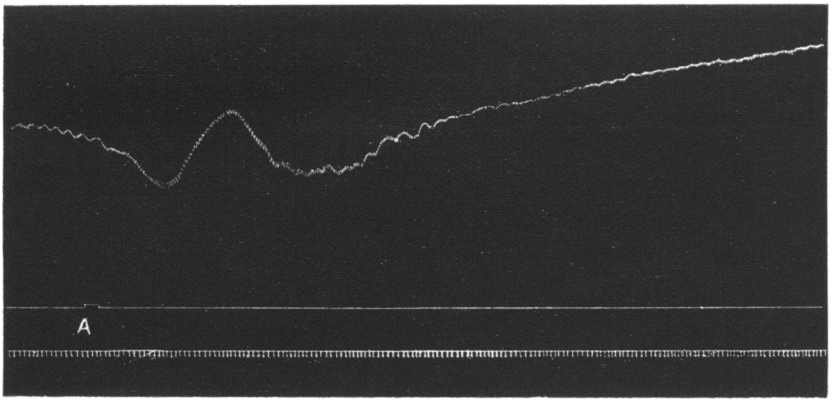

Fig. 4. Blood-pressure tracing of a cat, showing the effect of injecting a small quantity of anhalonnine. 2 c.c. of a 1 % solution injected at *A*.

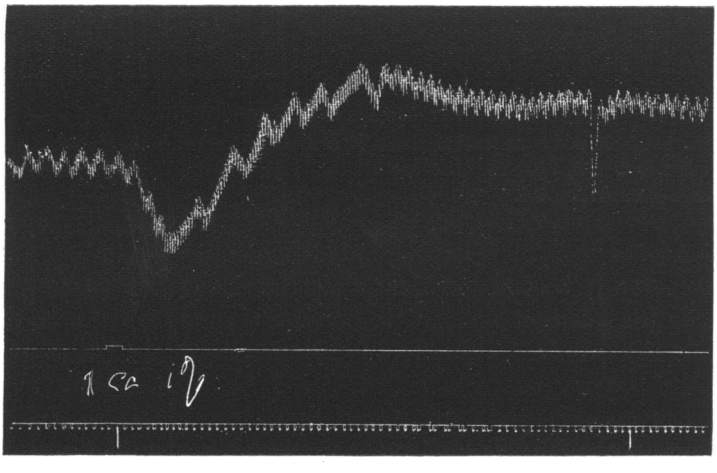

Fig. 5. Blood-pressure tracing of a cat, showing the effect of injecting 1 c.c. of a 1 % solution of lophophorine.

Should a large quantity have been injected, say ·04 gramme, the initial fall is greater and much more prolonged, and may even continue for half-an-hour or more: with this fall there is a much more marked

slowing of the heart. After a variable period there is a rise; this may either be gradual or more frequently sudden, as shown in Exp. V. (Fig. 6), the pressure exceeding the normal by from 10—20 mm. of mercury. After such an injection examination of the vagus shows it to be paralysed, generally completely, no amount of stimulation producing slowing or inhibition. If experiments be performed in which, simultaneously with the blood-pressure, the alterations in the vascu-

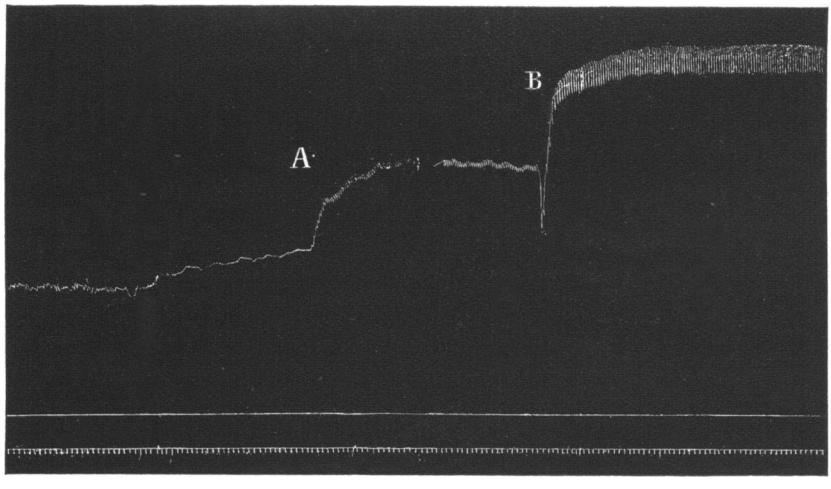

Fig. 6. Blood-pressure tracing of a cat (illustrating Exp. V.). At *A* 7½ mins. after an injection of ·05 grm. mezcaline there is a sudden rise of blood-pressure to about normal; and at *B*, 8½ mins. after the original injection the blood-pressure suddenly undergoes a further rise.

larisation of a loop of intestines are recorded by enclosing it in an air oncometer, it becomes evident that the changes of blood-pressure caused by the alkaloid are cardiac because the curve of the oncometer is an entirely passive one, following the curve of the blood-pressure. If, further, the nervous mechanism of the heart be paralysed by the injection of atropine, it is still found that, on administering the alkaloid, the typical effect is produced, *i.e.* the initial fall and subsequent rise in pressure with the cardiac slowing. All this evidence points to the conclusion that the main effect of these alkaloids is a direct one on cardiac muscle.

Another curious result was occasionally noticed in dogs after the subcutaneous injection of a large dose: 10 mins. after injection the face began to swell, and in half-an-hour's time œdema had rendered

it enormous, the lips and eyelids being greatly swollen; during this condition the heart was slow, and could barely be felt through the skin. One hour later the œdema had in every case disappeared, and the heart was quicker and very much stronger.

In man ·05 gramme lophophorine produces a marked slowing of the beat; in one case, in half-an-hour the beat was reduced from 70 to 55 per min.; with this slowing there is a rise in pressure with an apparently increased force of beat.

Muscular System. By isolating a frog's sartorius and painting with the standard solution no effect could be produced, the muscle reacting to stimuli normally as before.

Respiration. In moderate amounts no effect is produced on respiration, but in toxic quantities the respiration becomes quicker and shallower, death ultimately occurring from failure of the respiratory centre. In cats, after section of both vagi, a dose of the alkaloid, ordinarily sufficient to produce quickening, now has no effect. A still

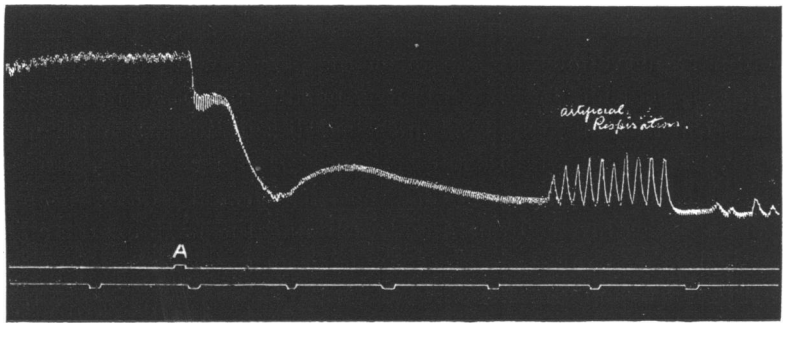

Fig. 7. Blood-pressure tracing of a cat. At *A* 2 c.c. of a 1% solution of lophophorine injected. Respiration immediately ceased and death resulted in 2½ mins. Vagi previously cut.

larger quantity, however, will nevertheless cause death by paralysing respiration (Fig. 7). In man the most serious result of an intoxicating dose is this effect on respiration, the breathing becomes shallower and more rapid, there are occasional long-drawn and deep sighs, and a painful feeling of suffocation is present.

Nervous System. It is for their curious effects on the nervous system that these alkaloids are most remarkable; very large doses, quite non-therapeutic in amount, are however required before the colour visions, etc. described by Mitchell are observed.

When a few drops of the standard solution are injected into the

lymph sac of a frog, the animal, after an interval of from 5 to 10 minutes, begins to walk about. In a short time it shows signs of paralysis, especially in the fore-limbs, so that when moving, these seem to be pushed forward by the hind. Paralysis is more marked in flexor than extensor muscles, the animal being able to extend its legs in the attempt to jump, but being unable to flex them again. Also in this condition slight irregular twitchings of muscles appear over the limbs and trunk, and the animal becomes exceedingly susceptible to stimuli, until the slightest touch or even breath of cold air is sufficient to give rise to a little nervous explosion, with the resulting contraction of several muscles. In a later stage (should the injection have been sufficiently large) there is complete paralysis, and an absence of the spontaneous twitchings, but the increased reflexes are still present. The frog now becomes gradually rigid, and the reflexes diminish until the rigidity is such that the whole body may be held out horizontally by simply supporting the legs, and peripheral stimulation produces no response. Stimulation of the sciatic nerve now produces a normal contraction, so that the effect must be central. If the nerve of an ordinary nerve-muscle preparation be placed with its end dipping into a $\frac{1}{2}\%$ solution for five minutes, no amount of stimulation will produce contraction, though the muscle still contracts when stimulated directly, an effect shown to be due to paralysis of nerve terminals.

If, whilst the frog is in the condition of increased reflex excitability, the brain is destroyed down to and including the medulla, the animal may still be thrown into a slight convulsion by a peripheral stimulation, although not to the same extent as before.

In mammalia the effect of intoxicating doses is highly characteristic. Cats generally exhibit a liking for the dark; they purr incessantly, and occasionally utter plaintive mews. This condition is followed by a soporific stage, in which the animal sits somewhat huddled together, with slightly dilated pupils, "fixedly staring," and it is only with difficulty that its attention can be arrested. All the reflexes are exaggerated, and there is considerable blunting of cutaneous sensation, whilst painful stimuli, such as pulling the ears, pinching the tail, or pricking with needles, are not noticed. The animal will not move unless compelled to do so, when it shows an ataxic gait, with jerky and very stiff movements; it keeps its legs widely apart, and, on coming to a standstill, shows a to-and-fro swaying movement, evidently the result of ataxia. In the same condition excessive starts occur as the result of stimuli, such, for example, as

dropping a weight, in which case the animal will also entirely fail to localise the sound.

When still further under the influence of the alkaloid, it becomes exceedingly difficult to rouse, and, besides the great incoordination of movement, shows definite signs of loss of power. It now lies in any position in which it is placed, the pupils are widely dilated, the eyes are closed, and the head drooping; no notice is taken of sound or cutaneous sensations, but it may be roused either through the sense of sight, taste, or smell. A little salt placed on the tongue, or carbon bisulphide near the nose, is sufficient to give rise to a momentary explosion of incoordinated movements over the whole body. Similarly, on raising the head and opening the eyes of a cat in front of a dog, no effect may be produced for an interval, but suddenly perception occurs, the dog is recognised as such, and a paroxysm of muscular movements is the result, the teeth showing, and the hair being erected, etc., to pass off, however, in two or three seconds, when the cat again lapses into its previous torpid condition. Irregular twitchings of muscles over the whole body may be seen, but are never troublesome or severe.

Occasionally, after an intoxicating dose, most of the physical elements of "terror" can be made out. The ears are drawn back, the hair over the body, especially the tail, becomes erected, there is twitching of the superficial muscles, the respiration being shallow and hurried, and the heart weak and irregular.

Herbivorous animals are less susceptible than carnivorous. In man[1] the nervous effects are extremely interesting, but on account of the respiratory depression which is liable to occur it is not desirable to experiment too freely; it is necessary to remember that this substance, like Indian hemp, varies considerably in its effects on different individuals, and that the element of idiosyncrasy is marked.

The pure alkaloid was dissolved in distilled water, and administered either by subcutaneous injection or by the mouth, in the former case the results being much more constant and certain.

The action may be divided into a preliminary stage and a stage of intoxication. In the former there is excitement, a feeling of exhilaration, and diminished kinæsthetic sensations, performances involving effort being hardly noticed, the face is flushed, and the pupils dilated; there is a tendency to talkativeness, which may become wandering later, when the patient begins to feel "light-headed."

[1] Experiments were only performed on two subjects.

This stage quickly passes away, and is followed by one of intoxication, in which there is a great inclination to lie down, although there is never any tendency to sleep. The pupils are now widely dilated, and act but sluggishly to light. On attempting to walk, the gait closely resembles that in alcoholic intoxication, and in all movements requiring precision the incoordination is evident. The body is generally in a tremulous condition, the tremors showing well when the attention is fixed on anything held in the hand. Reflexes over the whole body are much increased, including the skin reflexes, although there is considerable blunting of painful and tactile sensation. Twitching of muscles occurs in various parts of the body, especially noticeable in the face, and there is a curious feeling as if the face, lips, tongue, etc. were much swollen.

As in cannabis indica, time is over-estimated, possibly as a result of the rapid flow of ideas and the inability to fix the attention. Perception of space is also modified, on one occasion giving the impression that the ground sloped away in all directions.

Perception may be considerably delayed; for example, one may look at a person one knows well, and it is only after scanning his features for what appears to the experimenter a considerable time, that recognition occurs; it is possible, however, that this may be explained by the increased time-relation. The attention cannot be fixed, as the least stimulus is sufficient to alter the train of thought; thus it was found impossible to fix the attention on a book, and a subsequent examination of notes attempted during intoxication showed incoordination both as regards language and writing.

On two occasions when deeply under the influence of the drug, there was an indescribable feeling of dual existence; thus, after sitting with closed eyes subjectively examining the colour visions, on suddenly opening them for a brief space one seems to be a different self, as on waking from a dream we pass into a different world from that in which we have been. This may be to some extent comparable to the rhythmical rise and fall of the "physical waves" in Indian hemp intoxication.

But by far the most remarkable of these subjective phenomena are the sensory hallucinations, especially visual. These arise gradually, and are at first only seen with closed eyes: in the early stage (in my case) they closely resemble an attack of megrim[1], in that they show the same

[1] The colour visions occasionally seen in hysteria, neurasthenia, etc. may be compared to these.

undulatory motion of zigzagged lines. The visions rapidly become more marked, until on closing the eyes a regular kaleidoscopic play of colours can be seen with either eye, precisely the same; hence the condition must be central.

These colours may assume all kinds of fantastic shapes; they are never still, but constantly in motion, sometimes in a circular or to-and-fro manner, but more generally there is a kind of pulsation somewhat similar to that in the cinematograph. It is interesting to note that pressure to the eyeball was sufficient to alter the colours and change the type of vision. In no case were visions of external objects seen, but always the same dashes of colour, of a brilliance and blending which in the intoxicated condition one considered of indescribable beauty, and even as a memory still seem to possess a charm. The colouring of all external objects is intensified. The light blue shadows seen with the eyes open in this stage are, as suggested by Ellis, probably due to dilatation of the pupils[1]. Dobrowolsky[2] has shown that the dilatation of the pupils is necessary to such vision.

The effect of the sound of the piano was most curious and delightful, the whole air being filled with music, each note of which seemed to arrange around itself a medley of other notes which appeared to me to be surrounded by a halo of colour pulsating to the music.

Nasal hyperæsthesia was also present, though less evident than either the visual or auditory phenomena.

Urine. The drug is to some extent excreted by the kidneys, as was shown by the fact that ¾ of an hour after injection of ·2 gramme of the drug into a cat, 1 c.c. of the urine produced a typical effect on a frog. Control experiments showed that normal urine produced no effect.

All the alkaloids are distinctly diuretic. This is explained by observing their effect on the renal blood-pressure. If the kidney be placed in an oncometer and a tracing of the kidney volume be obtained together with the blood-pressure tracing, after an injection of one of the alkaloids it is seen that the effect on the renal vessels is passive. Hence the rise in pressure in the arteries which occurs after small doses will cause a rise in pressure in the renal blood vessels with resulting diuresis.

Differences between the alkaloids. Anhalonnine and anhalonidine have an action which seems to be the same in each case, but lophophorine, whilst behaving very similarly to these, is probably about

[1] Compare violet visions after eye operations.

[2] *Arch. für Ophthalmologie*, XXIII. p. 213.

twice as active: also the reflexes and automatic twitchings seem more marked in the case of lophophorine, suggesting its greater nervous

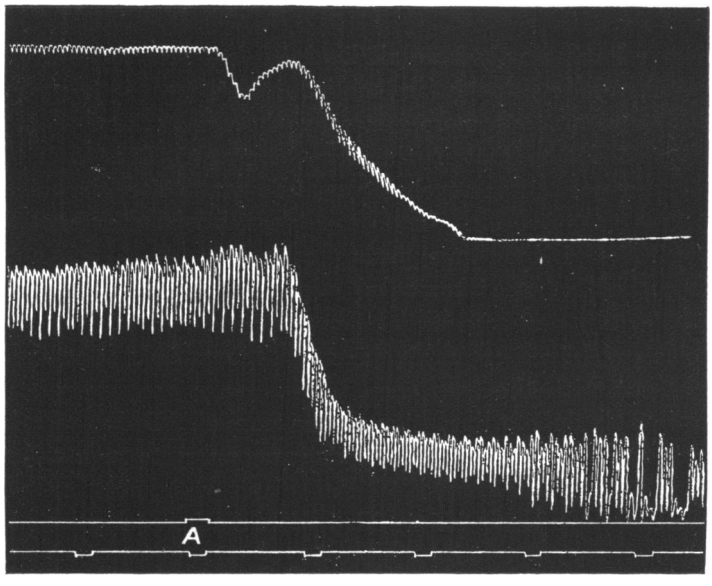

Fig. 8. Simultaneous tracing of the volume changes of the kidney and the blood-pressure of a dog. *A* represents the moment of injecting 10 c.c. of ·1% solution of anhalonnine. (The blood-pressure and kidney volume subsequently rose above normal.)

activity. As lophophorine differs only by the addition of CH_2 from anhalonnine and anhalonidine, and as it is extremely probable that it belongs to the same homologous series, this increased activity is remarkable.

Mezcaline, whilst agreeing precisely with the other alkaloids as regards cardiac and respiratory action, etc., appeared more effective in the production of colour visions.

After-effects. The only after-effect of serious import is the respiratory depression already mentioned. Circulatory depression also occurs, but is never so serious as the respiratory. Nausea is generally present after a large dose, but vomiting is rare. Headaches are seldom of serious importance, and when present are invariably described as being confined to the occipital region. From a considerable number of observations on myself, in only one case was an occipital headache produced, but then it lasted two days. Small administrations never produce unpleasant after-effects.

It must therefore be concluded that "Mescal" acts differently from any other known substance, although in isolated properties it resembles many. Cannabis indica, which at first it was thought most closely to resemble, differs from it in the delusions of merriment and in its hypnotic effect, whereas "Mescal" never gives rise to merriment, but rather to a condition of ideal content, and produces wakefulness.

To strychnine it is closely related by its marked effect on the brain and cord, but whereas strychnine acts mainly on the cord, the effect of "Mescal" is mainly cerebral and opisthotonos never occurs.

Nicotine it resembles in its effects on nerve, first paralysing nerve cells and then fibres.

Further of its properties may be compared to those of digitalis and cocaine, but in each case with marked contrasts. In its peculiar stimulation of the occipital cerebrum it appears to stand alone.

Its properties lead one to hope it may be of use in therapeutics: from the fact that even after very small doses a feeling of well-being and exhilaration results, points to its use as a general stimulant to the central nervous system, the diminution in the kinæsthetic sensations possibly making it of special use in melancholia. Further it is possible that its effect on slowing the heart by a direct action on cardiac muscle and in small doses increasing the force of the beat may be found of use.

TYPICAL ILLUSTRATIVE EXPERIMENTS.

Exp. I. Frog. Injected ·003 gramme anhalonnine (1% N.S.).

10 mins. Walking on toes. On jumping, fell on abdomen, with legs extended, which are drawn up afterwards.

30 mins. Fore limbs are almost completely paralysed, and when the animal moves these are pushed forward by the hind limbs. Cannot turn from the dorsal position. Reflexes increased. Irregular twitchings of the muscles.

60 mins. Complete paralysis, but a slight stimulation, such as a knock on table, or whiff of air, is sufficient to cause a small paroxysm of muscular contraction.

6 hours. Frog dead.

Exp. II. Frog, pithed and the heart and both vagi carefully exposed, and arrangements made to record the beats on a writing surface. Heart beating regularly 40 to minute. Either vagus on stimulation with secondary coil at 10 c.c. will completely inhibit the heart. 3 or 4 drops of 1% solution of alkaloid in normal saline dropped on heart.

1 min. Heart 34. Diastole drawn out.

3 mins. Heart 29. Stimulation of either vagus with the secondary coil at 10 cc. produces no effect and no strength of current is sufficient to produce inhibition. Stimulation of the sinus venosus at 15 c.c. gives rise to quickening of the heart.

30 mins. Heart 20, and stimulation sinus venosus now has no effect, even when secondary coil at 8 c.c.

Exp. III. Cat. Weight 1·84 kilos. Heart 180. Respiration 30. Injected subcutaneously ·08 gramme anhalonnine.

5 mins. Salivation marked, purring loudly, with occasional mewing.

15 mins. Lying down, and can only be made to move with difficulty. Eyes staring into space, fixed, dilated. Animal immoveable till disturbed.

20 mins. Heart forcible 136. Respiration 84, shallow. Mouth kept wide open, apparently to facilitate breathing.

30 mins. When walking shows marked ataxia, occasionally losing its balance whilst turning. Joints seem stiff, and the legs are held widely apart.

50 mins. Passed by bowels some liquid blood-stained mucoid material. Seems now quite incapable of walking. Reflexes increased. Cutaneous sensation much blunted. Heart 140, fairly strong. Respiration 110, very shallow.

1½ hours. Lying on side. Eyes immoveably fixed, and pupils widely dilated. Heart 190, irregular, occasionally dropping a beat. Respiration 164. Salivation still very marked. Hair over whole body and especially tail markedly erected.

Post mortem: Congestion of all abdominal viscera, liver, spleen, kidneys, mesentery, etc. Intestines, which contain some food, are quite normal, except for the last 6 ins. of rectum, which shows a marked hyperæmia, especially intense on the rugæ. This portion of intestines contains a trace of free blood. Bladder empty, and slightly congested.

The brain and cord both show a well-marked hyperæmia.

Exp. IV. Cat. Weight 2·18 kilos. Injected subcutaneously ·08 gramme anhalonnine. Previously heart 198, respiration 22.

15 mins. Exhibited a liking for dark. Considerable salivation. Occasional plaintive mews. Pupils slightly dilated. Remains fixedly staring at an object until dis-

turbed. Heart 180, respiration 63. Takes little or no notice of ear pulling, tail pinching, or other form of painful stimulation. Gait ataxic.

2 hours. Salivation. Heart 186, forcible. Respiration 45. On attempting to jump misses mark, and falls heavily. Reflexes increased. Pupils dilated and react but sluggishly to light. Very little notice taken of painful stimuli. Staring phenomena particularly well marked. Gives excessive starts on slight noises. When standing shows some to-and-fro movements.

3 hours. Heart 196, forcible. Respiration 68. Taking no notice of cutaneous stimuli. Incapable of standing. NaCl placed on tongue, or CS_2 or NH_3 put near to the nose act as a powerful stimulus, causing quite a paroxysm of movements. Similarly the presence of a dog, can the cat be made to recognise it as such, acts as a stimulus, giving rise to a spasm of incoordinate movements. Salivation still continues.

Subsequent history: Constipation for three days, and then a little diarrhœa. Refused food for 48 hours.

Exp. V. Cat. Weight 1·93 kilos. Anæsthetised, and arrangements made to record blood-pressure, respiration, time, etc. Heart 192, respiration 17. Injected ·05 gramme mezcaline into jugular vein. For half a minute there is a slight fall in pressure, followed immediately by a considerable rise, and the pressure continues high and has no subsequent marked fall.

1*st Injection.*

1 min. after. Heart 160, much stronger and more forcible. Respiration 11, slower and deeper.

5 mins. after. Heart 180, very strong. Respiration 18.

½ hour after. Heart 142. Respiration 10.

2*nd Injection.* Of ·05 gramme now given.

After which there is a short rise of pressure for about 40 seconds, followed by a very great fall.

2 mins. after. Heart 50. Very feeble. Respiration 13. Pressure very low for about 10 minutes, and it seemed as if the animal would die.

5 mins. after. Heart 98, very feeble, slow, and irregular. Respiration 10.

8½ mins. after. Without any warning there is a sudden rise of pressure to normal, with a considerably more active heart-beat.

9½ mins. after. A second sudden rise in pressure considerably above normal. Heart now beating 130 very vigorously. (See Fig. 6.)

Exp. VI. Healthy adult man. Weight 11 stones. ·25 gramme alkaloid taken by mouth (roughly an amount equivalent to two buttons), 12 o'clock. Before experiment pulse 73, respiration 17.

12.30 p.m. A strange feeling of exhilaration. Light-headed and restless, unable to read, as attention flags. Some salivation.

1 p.m. Feeling of nausea, some retching, but no vomiting.

1.30 p.m. Nausea still present, but not so marked. When sitting with closed eyes, balls of red fire pass slowly across field of vision. Later these changed to kaleidoscopic displays, with ever-varying colours, or revolving wheels of colour being arranged in a definite pattern, which constantly changes. Only seen with closed eyes. After-images are prolonged.

2 p.m. Pulse 55, strong. A peculiar feeling of stiffness noticed over head, scalp, lips, and cheeks. Visions have become more brilliant and real. They now consist largely of coloured lines crossing in all directions and mapping out ever-varying

patterns. Pressing the eyeball is often sufficient to alter the colours. The colouring of external objects appears particularly vivid, and some scent sprinkled on a handkerchief seemed at times peculiarly strong and penetrating. Pupils well dilated, and act sluggishly to light. Feel a strong desire to lie down.

2.30 p.m. Feeling of nausea quite disappeared, but there is a sense of oppression on the chest, and the respiration 35, shallow, with occasional deep sighs. I now experienced an extraordinary idea of unreality; I seemed to be having a dual existence—one in which I was subjective to all external and internal impressions (colour visions, etc.), and a second existence quite indescribable, in which I seemed to watch myself mentally in this subjective state. My hands now were tremulous; knee jerks increased. On walking I seemed to be "treading on air," and was ataxic. My voice became a little hoarse, auditory hyperæsthesia caused starting readily on slight noises. Intellection and introspection seemed to me unimpaired.

3 p.m. On seeing a friend I tried to be natural, but found myself asking him for the third time if he were all right. Fresh thoughts constantly rushed through my mind, and before I could complete a note I often forgot what I was writing about.

4 p.m. Took some food. Feeling more sober. My spirits very exuberant. Visions fading, respiration normal, heart 75.

10 p.m. Still some dilatation of the pupils, and the curious feeling of exhilaration.

After-effects were principally insomnia. No noticeable effect on bowels or urine.