appear to be more rapid at low temperatures than at high temperatures.

The whole question of the formation of solids at very low temperatures is of great interest both from a physical and from a biological standpoint. It is quite possible that if living organisms were cooled only to temperatures at which physical changes such as crystallisation take place with measurable velocity, the process would be fatal, whereas if they once were cooled to the temperature of liquid air, no such change could take place within finite time, and the organism would survive.*

These experiments were made in connection with some investigations which were being carried out at University College, London, with the assistance of a grant from the Royal Society. As I am at the moment unable to continue the work, I have decided to publish this note.

"A Contribution to the Study of the Action of Indian Cobra Poison."† By Captain R. H. ELLIOT, M.B., B.S. Lond., F.R.C.S. Eng., D.P.H. Camb., etc., of the Indian Medical Service (Madras). On special duty for Snake Venom Research under the orders of the Secretary of State for India. Communicated by Professor Sir THOMAS R. FRASER, F.R.S. Received January 18, —Read February 25, 1904.

(Abstract.)

Previous Work on the Subject.

Brunton and Fayrer‡ discussed the pharmacology of Cobra venom at some length; they attributed the effects of the poison to its action on the cerebro-spinal nerve-centres, especially on the respiratory centre. They observed that Cobra venom had a direct action on cardiac muscle, and that it also affected the heart through the vagal system, but they did not lay much stress on circulatory failure. They surmised that the high and maintained blood pressure of a cobraised animal was due to arteriolar constriction, but did not attempt to explain how this was brought about. Amongst the many other points of interest they took up, was the influence of artificial respiration in cobraism.

* Experimental results are given by Macfadyen, 'Roy. Soc. Proc.,' vol. 66, 1900, pp. 180, 339, 488; Swithinbank, 'Roy. Soc. Proc.,' vol. 68, 1901, p. 502.

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‡ 'Roy. Soc. Proc.,' vols. 21, 22, and 23.

Cunningham in the 'Scientific Memoirs by Medical Officers of the Army in India'* urged the opposing theory that Cobra venom acted on respiration, through the blood and not through the nervous system.

Weir Mitchell, and Reichert† carried on Brunton and Fayrer's views. Their paper was mainly concerned with the venoms of other snakes than the Cobra. They thought two factors were at work on the rate of the heart, viz., an increased activity of the accelerator centres, quickening the beat, and a direct action on the heart slowing it. They attributed the primary fall in blood pressure to depression of the vaso-motor centres, but thought it might be partly cardiac. The rise they considered "capillary" and the final fall cardiac.

Bagotzi‡ laid great stress on the *rôle* played by nerve-end paralyses (especially phrenic), and disputed Brunton's views that respiration was attacked through the medullary centre. He did not find any action of the venom on the vagal mechanism. He surmised that death with a tightly contracted heart, the result of very large doses of venom, was due to a cardiac action.

C. J. Martin in the article on snake venom in 'Allbutt's System of Medicine,' considers that, in Cobra poisoning, the circulatory mechanism is not easily affected, and contrasts this with the state of affairs in viperine poisoning. He found that vagal stimulations stopped the heart up to near the end of life in Cobra poisoning.

Object of this Research.

This was to accurately ascertain the precise part played by the various important centres, nerves and organs in the production of death from cobraism.

Methods employed in the Research.

1. *Perfusion of the frog vessels was carried out with solutions of Cobra venom of various strengths.*—The central nervous system had been destroyed first in each case.

The strength-limitation of the action of the venom on the arterioles was carefully studied.

2. *Perfusion of frog hearts was carried out with solutions of Cobra venom of various strengths.*—The isolated hearts were perfused in Schäfer's plethysmograph, and blood mixture was employed as the vehicle for the poison. The strength-limitation of the action of Cobra venom was again determined here. Certain drugs which resemble this poison in their action on heart muscle, were also experimented with, *e.g.*, strophanthin and the sulphate of atropia. The risks apparently

* 1895, Part IX, and 1898, Part XI.

† 'Smithsonian Contributions to Knowledge,' 1890.

‡ Virchow's 'Archiv für Path.,' vol. 122, p. 201.

attendant on the use of the latter drug in Cobra poisoning are pointed out.

3. *The study of the action of Cobra venom on the frog heart in situ* was next taken up, by means of a number of devices, which included the direct application of the poison to the medulla oblongata, which was exposed for the purpose.

4. *Perfusion of the mammalian heart was carried out with solutions of Cobra venom of various strengths.*—The isolated heart was perfused through its coronary vessels with a nutrient fluid, in which the venom was dissolved. Cats' and rabbits' hearts were used.

5. *By means of kymographic tracings, the blood pressure, respiratory movement, etc., of cobraised rabbits were recorded and studied.*—The activity of the vaso-motor mechanism was studied, in various stages of cobraism, by stimulations of the depressor and sciatic nerves, the vagi were cut, likewise at various stages, and their ends were also stimulated, in order to ascertain the part played in cobraism by the vagal inhibitory mechanism; injections of a solution of sulphate of atropine were also made, and the effects were observed. The author received much help in this section from Drs. Sillar and Prentice.

6. *A similar set of experiments to the last was carried out on dogs and cats, plethysmographic tracings of intestinal volume were also included here, in order to study the changes, if any, going on in the splanchnic area circulation.*

7. *The movements of the auricle and ventricle were studied in cobraised cats and dogs by removing the front of the chest parietes, and attaching the auricular and ventricular walls (by means of hooks and silk threads) to levers recording on a kymographic apparatus.*—The blood pressure in a large artery was recorded at the same time, and intestinal volume was also frequently taken by means of a plethysmograph. At various stages the vagi were divided or stimulated, and the results observed. The effect of giving further doses of Cobra venom with the vagi, intact or divided, was also studied. The condition of the vagal nerve-ends received close attention.

8. *By kymographic experiments the influence of artificial respiration on the centres, nerve-ends, etc., of cobraised animals was carefully studied.*—The experiments were varied in different ways.

9. *The direct action of Cobra venom on the respiratory centre of rabbits was tested by applying the poison to the exposed medulla oblongata.*—A stethograph recorded the respiratory movements, and the blood pressure was at the same time taken on the kymograph.

10. *Several series of experiments were undertaken to ascertain the part played by the phrenic and other nerve-ends* in producing the respiratory complications which are seen in cobraism.

Summary of Conclusions.

1. Cobra venom acts directly on the muscular tissue of the blood-vessels, or through their vaso-motor nerve-endings, constricting the arterioles, and thus raising the arterial blood pressure. It probably affects all organs alike. In the frog vessels the action can be traced down to dilutions of 1 : 10,000,000. In a Cobra-bitten man, the concentration of venom in the blood is probably at least thirty times as great as this.

2. Cobra venom also acts directly on the isolated frog ventricle, killing it in a position of firm systole, if the solution be concentrated, and stimulating it if a weaker strength be employed. The limit of the speedy lethal action on the isolated heart is reached at a concentration of about 1/500,000. The stimulating action can be traced down to a dilution of 1/10,000,000. This action of Cobra venom brings it into line with the glucosides of the strophanthin group. Its action is more rapid than that of strophanthin, and is certainly not inferior to it in strength. Atropine sulphate and Cobra venom, when acting in the same solution, intensify each other's action, and produce more summation of effect than one would have anticipated. This detracts from the value of the atropine salt in the treatment of cobraism, and makes it a dangerous remedy. The blood-pressure work has confirmed this view of the case.

3. Cobra venom powerfully affects the isolated mammalian heart, when solutions of it are perfused through the coronary circulation. The action appears to be a dual one, viz. (1) a direct action on the muscular fibre, or on the nerve endings, closely resembling that which is produced on the isolated frog ventricle; and (2) an action on the intracardiac vagal mechanism, which makes for inhibition. The result is that, in strong solutions, we find an irregular and extreme excitation of the heart, followed by early death in a position or systolic tone. If the concentration be less, the early stage of excitement yields to a prolonged phase, in which the tonic action of the poison on the heart is most pronounced: the beat is regular, steady, and strong. Cobra venom interferes with the circulation through the heart in a marked manner; this is probably due (1) to a constriction of the coronary vessels, brought about by the direct action of the venom on the vessel walls, and (2) to the condition of tonus into which the heart is tending to pass.

4. When given subcutaneously in low lethal doses, Cobra venom kills by paralysing the respiratory centre. Such a paralysis is under these circumstances gradually evolved, and in the early stages of the process there is often evidence of a phase of stimulation preceding the paretic phase.

There is a gradually increasing venosity of the blood, and in

consequence thereof all the harmful results of slow asphyxiation are produced.

If life is prolonged beyond the usual term by artificial respiration, and possibly also if the dose of venom is a very low lethal one which takes many hours to kill, the phrenic and other motor nerve-ends may become paralysed, but this is certainly not an essential feature of death from lethal doses of Cobra venom, which kill within five hours. I hope to make a farther communication on this subject later.

The convulsions which precede death are purely asphyxial, and can be at once stopped by artificial aëration of the blood. Each such convulsion is followed by a phase of exhaustion of the respiratory mechanism, which is almost certainly central.

If the dose of Cobra venom administered be a large one, and especially if it be given intravenously, the respiratory centre is quickly and severely affected, and respiration may cease almost at once. This cessation of breathing may be permanent, if artificial respiration be not quickly started, but if the dose be a smaller one, the rhythmic activity of the centre reasserts itself. At first there may be a number of deep spasmodic gasps, and then the movements of respiration re-begin, very gently at the commencement, and gaining force as time goes on, till a normal rhythm is re-established, or even a stage of stimulation is manifested. Soon, however, the centre fails again, and all the phenomena of asphyxiation appear.

By applying Cobra venom directly to the exposed medulla oblongata of the rabbit, I have shown that the respiratory centre can be paralysed without the phrenic nerve-ends or the heart being appreciably affected.

If very large doses of venom are injected, death may take place by cardiac failure, before the respiratory mechanism has given way. We have here to do with the direct action of the venom on the heart muscle; the beats become rapid, and shortened, and the heart passes into a systolic phase, in which it dies tightly contracted.

5. Cobra venom, when given in low lethal doses subcutaneously, raises the general blood pressure. There may be a slight preliminary fall before the rise, but often this is wanting. In the absence of farther interference the blood pressure remains high till very near the end of life. In the asphyxial convulsions which herald death, a farther steep rise of blood pressure takes place; this is soon followed by a sudden and very rapid fall to death.

The high level of blood pressure is due to—

1. The direct action of the circulating venom on the muscular tissue of the arterioles, causing a constriction of these vessels, and thus opposing a barrier to the onward flow of the blood;

2. The increased force of the heart beat as the outcome of the direct stimulating action of the venom on its muscular tissue, and

3. The stimulation of the vaso-motor centre, as a result of the steadily increasing venosity of the blood.

The slight preliminary fall of blood pressure, which is sometimes seen, is due to cardiac inhibition, but this subject will be reserved for discussion when dealing in the next section with the action of large doses of the poison.

The late fall in the rate of the heart beat is due to cardia inhibition, the latter is due to several factors.

1. A gradually progressive asphyxiation is taking place throughout such an experiment; this affects the vagal centre in common with the rest of the nervous system; the result is a stimulation of the inhibitory mechanism, and a consequent slowing and weakening of the heart.

2. The direct stimulating action of the venom on the vagal inhibitory centre acts in the same direction as the asphyxiation of the centre.

3. There is distinct evidence that even when the influence of the vagal centres is removed, inhibition of the heart continues to progress, though in a lessened degree. The obvious inference is that the vagal nerve-ends are stimulated by the circulating venom, and probably also as a result of deficient aëration of the blood.

4. It is not improbable that a stage of exhaustion of the heart muscle follows the early stimulative action of the venom; and

5. Exhaustion of the heart is probably predisposed to by the strain put upon the organ, in having to work for a long period against an abnormally high blood pressure.

We are now in a position to explain the sudden rapid fall of the curves of heart-beat rate and of blood pressure, which usher in death at the close of one of these long experiments. An over-strained and weakened heart is suddenly and violently called upon to bear a farther burden, for respiration has ceased and the medullary centres are acutely asphyxiated. As a consequence there is a violent excitation of the cardio-inhibitory and vaso-motor mechanisms. The heart is slowed and at the same time has to work against a suddenly increased pressure, and it gives way. In fact we have the phenomena of asphyxiation in their entirety.

The vessels of the splanchnic area are affected *pari passu* with those of the body generally, and they in no wise act independently. The vaso-motor mechanism remains active throughout, and is, as we have seen, profoundly affected by changes in the venosity of the blood.

6. Cobra venom, when injected in large doses and especially when given intravenously, causes—

(1) a sudden fall of blood pressure;

(2) a subsequent rise, provided the dose has not been too large; and

(3) a final fall to zero.

The early fall is undoubtedly due to inhibition of the heart. It has been clearly shown that this is mainly brought about by the direct action of the poison on the vagal centres in the medulla oblongata, as it occurs before the accompanying failure of respiration has had time to act. Moreover, it is seen whilst artificial respiration is being actively carried on, and can be checked under these circumstances by division of the vagi.

On the other hand, there can be no doubt that asphyxiation of the vago-inhibitory centre intensifies and maintains the inhibition which direct influence of the venom on the vagal centre produces.

The spontaneous recovery of respiration, or the application of artificial respiration, has a powerful influence in mitigating the action of the venom on the vagal centre. In the same way artificial respiration, and to a less extent the spontaneous recovery of respiration, appear to act beneficially on the poisoned respiratory centre.

Even if the heart is cut adrift from all central vagal impulses, whether direct or indirect, by the division of the vagi, there yet remains evidence of a continued inhibition which must be attributed to the direct action of Cobra venom on the terminals of the vago-inhibitory mechanism. This action would appear to be a direct one, but there is every probability that it is indirect as well, in other words that it acts through asphyxiation of the vagal terminals, as well as by the poisoning of these parts by the circulating poison. There is, however, another factor which must not be lost sight of, viz., a direct exhaustion of the heart muscle as the result of irregular over-stimulation.

2. When the secondary rise of blood pressure, which follows the primary fall, occurs, it is due to the same factors which determine its occurrence when small doses have been injected. It remains to explain why it is sometimes absent, brief or ill marked. The explanation is simple; it is merely a question of cardiac failure. We have seen that the direct inhibitory action of the venom through the vagal centre is capable of overcoming the tendency which the blood circulating through the heart muscle has to throw that muscle into death in systolic tone. Were it not for these two rival forces to some extent equilibrating each other, Cobra poison would kill by its direct action on the heart muscle. When the doses are comparatively small, or when the vagi are cut or thrown out of gear by atropine, we find the tonic cardio-muscular influence of the venom in evidence, but when the dose of venom is a large, and especially when it is intravenously given (the vagi remaining intact), the inhibitory action overpowers the muscular excitation, and failure of the heart occurs. If the inhibition is sufficiently well marked, no amount of arteriolar spasm that occurs will compensate it, consequently the blood pressure falls.

When the dose of venom is a very large one, the direct muscular

stimulation may be so intense as to overcome the maximum inhibitory impulse, and then the heart dies in systole with a quickened beat, and is found after death as hard as a contracted *post-partum* uterus. Under such circumstances, any increase in the force of the heart is temporary, for the beat is probably a very partial one, the heart passes through a stage of excitement into one of increasing systolic tonus, in which the contractions are very limited in extent.

Acknowledgments.

In conclusion, I desire to express my indebtedness to all who have so ungrudgingly helped me in my work. I owe my thanks to one and all of Sir Thomas Fraser's and Professor Schäfer's assistants, but especially to Drs. Sillar, Carmichael, and Hering, who were always willing to aid me in any way in their power. Messrs. Burnett, Jolly, and Locherby, who gave up much of their time to work regularly for me as my volunteer assistants, did excellent work throughout, and I most gratefully acknowledge that, but for their aid, the work could not have been done in the time.

The help given me by Sir Thomas Fraser and by Professor Schäfer I have already acknowledged. It is not possible for me to do justice to it, or to the unvarying kindness I met with from them both.

Lastly, but far from least, my acknowledgments are due to the Secretary of State for India, to the Government of India, and to the Government of Madras, for the opportunity that has been given me to carry out this work.