is poisonous because of its affinity for hæmoglobin, taking the place which oxygen occupies in the normal process of aëration of the blood. This affinity of carbonic oxide for hæmoglobin is almost exactly 300 times as great as that of oxygen. A sample of blood in a flask exposed to air containing 0.07 per cent. carbonic oxide, and shaken well up so as to absorb the gases until the hæmoglobin is completely saturated, will, when examined, be found 50 per cent. saturated with oxygen and 50 per cent. saturated with carbonic oxide. Similarly, if we breathe air containing 0.06 to 0.07 per cent. carbonic oxide, the hæmoglobin becomes equally saturated with oxygen and carbonic oxide. Speaking generally, the larger the percentage of carbonic oxide present in the air the higher the resulting saturation with this gas. The limit for the circulating blood is reached when its hæmoglobin is so highly saturated with carbonic oxide as to be unable to carry sufficient oxygen to support life. The first case in the series had reached the highest limit which has been observed (83 per cent.). The patient in this case had survived until only 17 per cent. of the total oxygen-carrying power of the hæmoglobin was left unoccupied by the carbonic oxide. The other percentage in the cases is distinctly lower. The same variation in saturation, however, is observed in the blood of coal miners who have died from the carbonic oxide resulting from an explosion in the pit.²

Since the most important point in such cases is the saturation of the hæmoglobin by the carbonic oxide, it may be well to refer to the method by which it is estimated. The carmine method was first described by Haldane.³ The colour of a dilute solution of blood in the normal condition is yellow, but if carbonic oxide be combined with the hæmoglobin it is pink. The intensity of the pink colour in a given sample depends on the relative proportions of carboxyhæmoglobin and oxyhæmoglobin present. It is possible by adding a dilute solution of carmine to normal blood to give it the pink colour of the blood containing carbonic oxide, and if the carmine solution be added from a burette we can measure the amount needed to give a pink of the same intensity as that due to any given saturation with carbonic oxide.

As regards the pathology of the condition, two facts of importance must be kept in view. The first is the effect of the saturation of the hæmoglobin with carbonic oxide is equivalent to that of depriving a person of oxygen by decreasing the amount in the air breathed. The patient poisoned by gas actually suffers from a form of suffocation. When a person exposed to carbonic oxide is found while still breathing and placed in normal air the carbonic oxide is gradually eliminated from the blood so that after some hours it has completely disappeared. The eliminating force is the affinity of the oxygen for the hæmoglobin. This gradually displaces the carbonic oxide, and the higher the percentage of oxygen the quicker the elimination. The case of the child No. 5 is of importance because it is the first on record in which it was proved that in three hours practically the whole of the carbonic oxide had been eliminated from the blood. In any case, when urgent symptoms of suffocation are present, pure oxygen should be administered, or if this cannot be procured, artificial respiration should be performed. It is desirable that the patient should remain as short a time as possible under the influence of the carbonic oxide, and for this reason oxygen should be administered even when the sole advantage would be a hastening of the recovery.

To the second fact—the after-effect on the patient of being nearly suffocated—I wish to call special attention, since it forms the real problem with which a physician has to deal. The more important elements of the after-effect are as follows:

1. A most important effect which the deprivation of oxygen has on animals is a fall in the body temperature. This is especially true of very small animals, such as mice; it is probably also true of man. The patient, if cold, should be warmed as rapidly as possible by the ordinary means, applied externally and internally. It has been noted by Haldane that after an explosion in a coal mine the men are often observed to become unconscious or even to die suddenly when they reach the outside air. The comparative coldness of the fresh air is in all probability an important factor in producing this sudden effect. Again cases are recorded in which the temperature has risen before death, suggesting that the nerve tissues concerned in regulating the body heat have been

seriously damaged by the deprivation of oxygen. In this condition of the nervous system the effect of cold air may be greatly exaggerated.

2. When the blood is over 30 per cent. saturated with carbonic oxide even slight muscular exercise such as walking produces violent headache, and if the saturation be a little higher the exercise unless extremely moderate causes the person to become giddy and unable to proceed. In the record of the cases Nos. 2 and 3 I mentioned that a young man in the next room had suffered from the effects of the gas, but that at first he was able to walk about and yet did not recover for over twenty-four hours. The probability is that he aggravated his condition by the exertions he made. When the blood is highly saturated with carbonic oxide treatment should include complete rest. Any exertion causes a drain on the available oxygen, and when this is much reduced the smallest additional drain is probably very serious. A most valuable account of the effects of exertion on those poisoned by carbonic oxide will be found in the Blue Book on the Snaefell Mining Disaster. An abstract of this report was given in the BRITISH MEDICAL JOURNAL of July 2nd, 1898.

3. An increased excitability of the nervous system is seen in the convulsions or tetanic spasms which occur. Effects of this nature have been obtained by the partial suffocation of animals, and it is not infrequently the case that patients die from damage to the nervous system hours, or it may be days, after they have been removed from the gas. On this question interesting notes will be found in Dr. Shaw Lyttle's Appendix to Haldane's Report on Colliery Explosions, 1896.

4. The heart is frequently affected. Dr. Tomb remarks that the great source of difficulty in the case he treated (No. 5) was the condition of the heart.

5. More remote effects still have to be noted. Dr. J. R. Davison, of Belfast, described a case of gas poisoning in which the patient died after four days from pneumonia. This patient never completely recovered consciousness. Part of the general damage which the suffocation had caused was a lowering of the normal resistance to the pneumococcus.⁴

The fact on which all the symptoms depend is the deprivation of oxygen. The mechanism of the circulation and various nerve centres are affected because they continue in activity, during the period of suffocation, at approximately the normal rate, while the available oxygen has been reduced to a minimum. This doubtless causes in the living tissues profound pathological changes. The nature of these changes is unknown apart from their functional manifestations.

REFERENCES.

¹ Report of the Committee, 1899, Appendix 7. ² Vide Haldane's Report on the Causes of Death in Colliery Explosions, 1896. ³ *Journal of Physiology*, vol. xviii, p. 430. ⁴ Report of Carlisle meeting of British Medical Association, 1896.

THE NEUTRALISING POWER OF CALMETTE'S ANTIVENOMOUS SERUM: ITS VALUE IN THE TREATMENT OF SNAKEBITE.

BY

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It will perhaps be well to state at the outset that it is not our intention in this paper to enter into the controversy as to the nature of the antagonism between snake venom and antivenomous serum, but to confine ourselves to detailing the experiments which we have performed under Professor Wright's direction with a view to determining what is the amount of venom which a given quantity of serum is capable of neutralising. We propose further to consider the question of the application of our results to the practical therapeutics of snakebite. The method¹ which M. Calmette recommends for estimating the antitoxic power of his serum is briefly stated as follows: The dose of venom which will kill a rabbit of 2 kilos. weight in from 15 to 20 minutes, when injected into the marginal vein of the ear, is determined; then the minimum amount of serum which will prevent death when

injected intravenously five minutes before this dose is ascertained; this is done by experimenting with varying quantities of serum. If 1 c.cm. is able to accomplish this, M. Calmette says that the serum contains 2,000 immunity units per c.cm., or 20,000 per 10 c.cm.

The objection which may be taken to this method is that there is no direct estimation of the amount of venom which a given quantity of serum will neutralise, inasmuch as no account is taken of the fact that the untreated animal is capable of surviving the injection of a certain quantity of venom.

Let us consider this point still further. Martin² of Melbourne, in some observations (to be more fully referred to later on) with the poison of the Australian tiger snake (*hoplocephalus curtus*) used in his earlier experiments only a single fatal dose of venom in estimating the curative value of Calmette's serum. However, in a later publication³ he recognised that this method was fallacious, inasmuch as if the amount of serum injected is able to neutralise even a mere fraction of the single lethal dose the animal will survive, even though the larger part of the venom remains unneutralised. He therefore recommends the employment of at least ten lethal doses.

This method of employing as a test dose a large multiple of the minimum fatal dose is employed also in estimating the value of other antitoxic serums. In the case, for instance, of diphtheria antitoxin, the test dose which is employed by Behring consists of ten lethal doses, while the test dose which is now employed by Ehrlich consists of 100 lethal doses. We may, therefore, take it as generally recognised that some known multiple of the lethal dose must always be employed in standardising any antitoxin.

When this multiple is a small one, in order to arrive at as accurate an estimation as possible of the neutralising power of the antitoxin, it is necessary to deduct from the amount of toxin which has been injected the maximum dose of toxin under which the animal can survive. An illustration will perhaps make this more obvious: Supposing we have found that 0.3 mgrm. of a particular toxin is the maximum non-lethal dose for an animal, and supposing we have found that 0.35 mgrm. is the minimum lethal dose, and supposing further that 1 c.cm. of a particular serum is the smallest quantity which will prevent death, when the test dose, consisting of 3.5 mgrm. (ten lethal doses) is used, we are then, bearing in mind that the animal is capable of surviving the injection of 0.3 mgrm., only justified in saying that 1 c.cm. of serum is capable of neutralising at least $3.5 - 0.3$ mgrm. = 3.2 mgrm., but we are not entitled to infer that the 1 c.cm. of serum is capable of neutralising the total amount which has been injected.

Professor Fraser,⁴ of Edinburgh, has furnished us with an example which illustrates the necessity of attending to this point. Working with cobra venom and a serum which he had himself prepared, he found that the minimum lethal dose of the venom was 0.000245 gram per kilo. of rabbit; from this we are justified in inferring that a rabbit would be able to survive the injection of at least 0.0002 gram per kilo. He then estimated the minimum amount of serum which would prevent death when mixed *in vitro* with different multiples of the lethal dose. Leaving out for reasons previously stated the experiments in which very small multiples of a lethal dose were employed, we may tabulate his results as follows:

1.	4 lethal doses required	1.2 c.cm.
2.	5 " " "	1.5 c.cm.
3.	8 " " "	2.5 c.cm.
4.	10 " " "	3.4 c.cm.

If we in each case deduct the amount of venom, namely, 0.0002 gram, which may be injected without fatal results, an easy calculation will enable us to arrive at the result that 1 c.cm. of the serum has in the successive experiments neutralised at least 0.0005 gram, 0.00068 gram, 0.0007 gram, and 0.00066 gram.

When the test dose of toxin consists of a high multiple of the lethal dose, as for instance in the case of Ehrlich's method of estimating the strength of diphtheria antitoxin, the test dose consists of 100 lethal doses, the deduction which has to be made for possibly non-neutralised toxin may for all practical purposes be omitted. For in such a case the certainly neutralised toxin obviously stands in the relation of 99 to 1 to the possibly non-neutralised toxin. From experiments which we have made with a mixture of cobra and viperine

venom (Series I of protocols), as used by M. Calmette to standardise his serum, we have ascertained that the amount of venom which kills a rabbit in about twenty minutes, when injected into the marginal vein of the ear, is about three times the lethal dose. We have seen that this is the amount which M. Calmette recommends to test the curative power of his serum. It is therefore obvious from what we have said above that the amount of serum required to prevent death will in this case be that amount which is capable of neutralising something over two lethal doses of venom. Hence in estimating the amount of venom which the serum has neutralised we have to deduct from the three lethal doses which are employed by Calmette the quantity of venom which constitutes the maximum non-lethal dose.

Keeping these points in view, we may now pass on to see what values have been obtained for Calmette's serum by other observers, by M. Calmette, and by ourselves. In Martin's first experiments² with the poison of *hoplocephalus curtus* he found that 1 c.cm. of Calmette's serum was able to counteract 0.0001 gram of a previously heated venom.⁵ In these experiments the serum was injected into the jugular vein one hour previously to the injection of the poison which was given hypodermically in the flank. But, inasmuch as in this series only one lethal dose was used as a test dose, and inasmuch as experiments with one lethal dose are subject to the fallacies which have been explained above, it will be obvious that we cannot attribute any value to this set of test experiments.

In later experiments⁶ Martin and Cherry, working this time with eight lethal doses of the same poison, have found that 1.5 c.cm. of serum, when mixed *in vitro* with the poison, is able to counteract this test dose; they have also shown that for rabbits the minimum lethal dose of this venom, when deprived of one of its constituents by heat, is 0.000025 gram per kilo., animals being able to survive a dose of 0.00002 gram. We can, therefore, say that 1.5 c.cm. is able to neutralise at least 0.00018 gram, namely, that 1 c.cm. can neutralise at least 0.00012 gram. In the same series of experiments they have found that 1 c.cm. fails to neutralise the eight lethal doses, so that in this case we can say that 1 c.cm. fails to neutralise 0.00018 gram. From this it is obvious that 1 c.cm. of Calmette's serum neutralises something between 0.00012 gram and 0.00018 gram of the venom of this particular snake.

M. Calmette states that the serum which he is issuing from the Institute at Lille possesses 20,000 immunity units per 10 c.cm. by his notation, or, in other words, that 1 c.cm. injected intravenously in a 2 kilo. rabbit five minutes before the venom is able to counteract a dose which would kill a control rabbit in from fifteen to twenty minutes. In our experiments (Series I of protocols) we have shown that the lethal dose of the mixed venom with which we worked, and which M. Calmette himself uses to control his serum, is 0.00035 gram per kilo., 0.00025 gram per kilo. being the maximum non-lethal dose. We have shown also that the dose which kills a 2 kilo. rabbit in about twenty minutes is equal to three lethal doses, namely, 0.002 gram. It is therefore obvious that 1 c.cm. of a serum which contains 20,000 of Calmette's immunity units per 10 c.cm. would have to neutralise at least 0.002 (that is, three lethal doses for a 2 kilo. rabbit) = 0.0005 (that is, the maximum non-lethal dose for a 2 kilo. rabbit) = 0.0015 gram of venom to prevent the death of the animal. This then expressed in weight of snake venom is the neutralising power which M. Calmette attributes to his serum.

The series of experiments which we have now to present, and which are detailed in the protocols, were made with a direct view of controlling the statement of M. Calmette. They were made with a mixed colubrine and viperine venom, which was supplied to us by M. Calmette. We take this opportunity of thanking M. Calmette for his kindness in giving us this, as well as an ample supply of his antivenomous serum.

We may preface the protocols of our experiments by giving a short account of the methods employed and the general results obtained.

A solution of the dried venom of strength 1 per cent. was made in sterile water. This was heated to 73° C., and was kept at that temperature for half an hour in order to precipitate the coagulable proteid. This was done with a view of

testing the antidotal power of the serum upon a venom, which is in every respect identical with the venom which is employed by M. Calmette in immunising his horses. It was then filtered to separate out this substance. Rabbits were the animals used, and all injections were made into the marginal vein of the ear.

Series I was undertaken to determine the minimum lethal dose. A certain lethal dose was found to be 0.00035 gram per kilo., and the maximum non-lethal dose was found to be 0.00025 gram per kilo.; 0.0003 gram per kilo. was on one occasion lethal, on another occasion not so.

In the second series, six times the minimum lethal dose—namely, 0.002 gram per kilo, a quantity which killed the control animal in three minutes—was used. This amount was mixed *in vitro* with varying amounts of serum. The mixture was allowed to stand at the laboratory temperature (about 18° C.) for half an hour. It was then injected, as in the previous series, into the marginal vein of the ear. By referring to this series in the protocols, it will be seen that 1 c.cm. of serum failed to counteract the six lethal doses, while 1.25 c.cm. accomplished this object. We have therefore arrived at the result that 1 c.cm. of serum fails to neutralise 0.002 gram—0.00025 gram=0.00175 gram, while 1.25 c.cm. is able to neutralise this amount at least—namely, that 1 c.cm. can neutralise at least 0.0014 gram, while it fails to neutralise 0.00175 gram.

In Series III experiments were made to ascertain what was the neutralising power of the serum when injected five minutes before the venom. The same quantity of venom was used as in the last series. Practically the same results were obtained in this case as when the mixture was made *in vitro*. For purposes of our inquiries into the therapeutical value of the serum we shall take it that 1 c.cm. is able to neutralise 0.0015 gram of this mixed venom. This result, which we have obtained in our experiments, exactly confirms Calmette. When we try to reconcile this result with that of Martin and Cherry, working with the poison of *hoplocephalus curtus*, it is only necessary to point out that we are using as our test venom a venom identical in all points with the venom employed in immunising, whereas Martin and Cherry were using quite another venom, and one which, judging from the lethal dose, was ten times more deadly.

We shall now pass on to see what practical bearing this has on the treatment of snakebite. To do this we shall best serve our purpose by considering the specific case of a bite from a cobra. M. Calmette⁷ has shown that for the rabbit the minimum fatal dose of dried cobra venom is on an average 0.00025 gram per kilo. We may say, therefore, that 0.0002 gram is a quantity which a kilo. of rabbit can just endure without succumbing to its effects. Now we have seen that 1 c.cm. of serum is able to neutralise 0.0015 gram of a venom, the fatal dose of which is 0.00035 gram per kilo. We are, therefore, even assuming that cobra venom is a third more deadly than the venom we employed, justified in calculating that 1 c.cm. of serum is able to neutralise about 0.001 gram of cobra poison.

M. Calmette⁸ has further shown that a good-sized cobra injects at each bite a quantity of venom which in the dried state amounts to from 0.03 to 0.045 gram. Now if man were equally susceptible weight for weight as the rabbit (man is, in all probability, much less susceptible), the maximum non-lethal dose for a 60 kilo. man would obviously be 0.012 gram. If we take 0.04 gram as an average amount of venom injected, it is obvious that the minimum amount of serum which would have to be administered in order to save life would be the quantum which would suffice to neutralise 0.04—0.012 gram=0.028 gram. We have assumed that 1 c.cm. of serum is able to neutralise 0.001 gram of dried cobra venom. It would therefore follow upon this assumption that 28 c.cm. of serum would have to be administered. The following facts, however, go to prove that man enjoys a higher degree of insusceptibility than the rabbit, and that, in consequence, a less quantity than 28 c.cm. would have to be administered.

1. Calmette⁹ has proved that it takes twice the amount of venom to kill 500 grams of rabbit that it does to kill 500 grams of guinea-pig; also that the quantity which would kill 12 kilos. of rabbit in three hours takes twelve hours to kill a dog of 7 kilos. The same law holds good as regards the monkey and the ass. It seems therefore to follow that the larger the

animal the more venom is required to kill weight for weight.

2. Fayrer, in his statistics on the percentage of deaths following bites of the Indian venomous snakes, states that only 25 to 35 per cent. of those bitten die, and that the average time in which death occurs is from 6 to 12 hours. Now, if man were as susceptible as the rabbit the fatal dose for a 60 kilo. man would be 0.038 gram of cobra venom. No cobra ever gives less than 0.019 gram at each bite,⁸ the average as we have seen being 0.03 to 0.045 gram. It follows that if man were equally susceptible every untreated case of cobra bite would prove fatal, instead of only 25 to 35 per cent. of the total number. We may therefore conclude that man is not as susceptible as the rabbit, weight for weight.

Fraser¹⁰ estimates that the lethal dose for a man of 60 kilos. is 0.0317 gram. That this is probably fairly correct is evident from the data which have been given above. If so, we may take 0.03 gram as the maximum non-lethal dose for an average man. Working on these assumptions, and taking in this case the maximum amount which a cobra can inject, namely, 0.045 gram, we can calculate that the amount of serum required to secure survival of bitten persons would be the amount which is able to neutralise 0.045—0.03 gram.=0.015 gram. We have assumed that 1 c.cm. can neutralise 0.001 gram of cobra venom; we should, therefore require for this amount 15 c.cm. of serum.

Objection will probably be taken to this conclusion, inasmuch as it is founded on experiments in which the serum has been mixed *in vitro* with the venom, or has been injected into the blood stream before the venom. A moment's consideration, however, will show that if we treat a case of snakebite by an intravenous injection of antivenomous serum, soon after the inoculation, we are practically repeating in man the experiments which we have detailed in Series III of protocols. Leaving out of consideration the cases in which death takes place very rapidly after inoculation (in these the poison is probably injected directly into a vessel), we may consider what happens in the commoner type of case in which death does not take place till some hours after the bite. During this interval the poison is being absorbed gradually. That this is not an extremely rapid process is evident from the experiments by which M. Calmette¹¹ has demonstrated the therapeutical value of the alkaline hypochlorites. An animal inoculated hypodermically with a dose of venom, which would kill the control in less than two hours, can be saved by injecting, up to half an hour afterwards, a solution of the hypochlorite of calcium all round the site of inoculation. If the injection of the hypochlorite is given intravenously instead of round the site of inoculation, the animal dies. Here there is, therefore, no doubt that the hypochlorite acts by destroying locally the poison which has not yet been absorbed, and that the amount which has been absorbed in the half-hour is not sufficient to kill the animal.

If, then, we introduce over 15 c.cm. of antivenomous serum into the blood before the lapse of such period of time as may be required for the absorption of the full lethal dose of venom, we may obviously expect to achieve the result we have in view, and to save our patient. It is evident, then, that we have in Calmette's serum a remedy which, if employed in the dose and manner stated above, should prove efficacious in all cases of bites from cobras and other poisonous snakes.

PROTOCOLS.

I.—Experiments to determine the Minimum Lethal Dose of Venom.

Animal.	Weight in Grams.	Amount of Venom per kilo. of Body Weight in Grams.	Result.
Rabbit 1 ...	1450	0.002000	Died in 3 minutes.
Rabbit 2 ...	1650	0.001000	Died in 21 minutes.
Rabbit 3 ...	1220	0.000500	Died in 45 minutes.
Rabbit 4 ...	1115	0.000350	Died in 55 minutes.
Rabbit 5 ...	2345	0.000300	Found dead 40 hours afterwards.
Rabbit 6 ...	1070	0.000300	Very ill for 2 days; lost 40 grams weight.
Rabbit 7 ...	980	0.000250	Very ill for 2 days; lost 80 grams weight.
Rabbit 8 ...	1070	0.000200	Ill for 2 days; lost 15 grams weight.
Rabbit 9 ...	2045	0.000125	No symptoms.

The poison used was a mixture of colubrine and viperine venom. In the first instance a 1 per cent. solution in sterile water was made. This solution was heated to 73° C., and kept at that temperature for half an hour; it was then filtered. When necessary a tenfold dilution of the original solution was used. The weights refer to the original dried venom. All injections were made into the marginal vein of the ear. It appears from this that 0.00035 gram per kilo. is a certain lethal dose; that 0.00030 gram per kilo. is a doubtful lethal dose, while 0.00025 gram per kilo. is a dose which a rabbit can survive under, a maximum non-lethal dose.

II.—Experiments to ascertain the amount of Venom which 1 c.cm. of Calmette's Serum is capable of Neutralising, the Venom and Serum being mixed *in vitro*.

In this series six lethal doses, namely, 0.002 gram per kilo., were mixed with varying amounts of serum. The mixture was allowed to stand at the laboratory temperature (18° C.) for half an hour, and was then injected into the marginal vein of the ear. The venom was the same solution as was used in Series I. In calculating the amount of venom which the serum had been able to neutralise, or had failed to neutralise, the maximum non-lethal dose, namely, 0.00025 gram per kilo. was deducted in all cases.

Animal.	Weight in Grams.	Amount of Venom per kilo. of Body Weight in Grams.	Amount of Serum per kilo. of Body Weight in c.cm.	Result.
Rabbit 1 ...	1280	0.002	1.50	No symptoms.
Rabbit 2 ...	1705	0.002	1.25	No symptoms.
Rabbit 3 ...	1980	0.002	1.25	No symptoms.
Rabbit 4 ...	1977	0.002	1.00	Found dead four hours afterwards.

From the above series we conclude that 1 c.cm. of serum fails to neutralise 0.002 — 0.00025 gram = 0.00175 gram, while 1.25 c.cm. can neutralise this amount at least, namely, that 1 c.cm. is able to neutralise 0.0014 gram at least.

III.—Experiments to ascertain the amount of Venom which 1 c.cm. of Serum is capable of Neutralising, the Serum being Injected five minutes before the Venom.

Six lethal doses of venom were used as before. Injections were made into the marginal veins of the ears.

Animal.	Weight in Grams.	Amount of Venom per kilo. of Body Weight in Grams.	Amount of Serum per kilo. of Body Weight in c.cm.	Result.
Rabbit 1 ...	1150	0.002	2.00	No symptoms.
Rabbit 2 ...	1290	0.002	1.50	Ill for 2 days; lost 16 grams weight.
Rabbit 3 ...	1050	0.002	1.25	Very ill for 2 days; lost 40 grams weight.
Rabbit 4 ...	1700	0.002	1.25	Very ill for 2 days; lost 85 grams weight.
Rabbit 5 ...	1400	0.002	1.00	Died in 60 minutes.
Rabbit 6 ...	2490	0.002	0.50	Died in 25 minutes.

The results obtained from this series are practically the same as from Series II. It will be noticed that the rabbits Nos. 2, 3, and 4 showed marked symptoms and were ill for some time, while the rabbits in Series II which received corresponding amounts of venom and serum, mixed and kept for half an hour *in vitro*, showed no symptoms. This, perhaps, may be explained by the fact pointed out by Martin and Cherry⁶ that, owing to the large molecular size and complexity of these substances, a certain interval of time must elapse before any chemical reaction is complete between them. During this interval an amount of venom sufficient to give rise to some symptoms of poisoning may pass into the central nervous system.

NOTE AND REFERENCES.

¹ Ann. de l'Inst. Pasteur, 1897, p. 225. ² Intercolonial Medical Journal of Australasia, August 20th, 1897. ³ Ibid., April 20th, 1898. ⁴ BRITISH MEDICAL JOURNAL, 1895, p. 1310; and 1896, p. 957. ⁵ The venom is heated to coagulate a coagulable proteid, which is then filtered out. It is the non-coagulable residue which Calmette uses to immunise his horses. The coagulable proteid has been proved to destroy the blood corpuscles, and to produce intravascular clotting if it reaches the circulation rapidly. The non-coagulable proteid affects principally the central nervous system. ⁶ BRITISH MEDICAL JOURNAL, 1898, p. 1120. ⁷ Calmette, Le Venin des Serpents, p. 25. ⁸ Loc. cit., p. 18. ⁹ Loc. cit., p. 26. ¹⁰ BRITISH MEDICAL JOURNAL, 1896, p. 957. ¹¹ Calmette, Le Venin des Serpents, p. 36.

A CASE OF GENERAL PARALYSIS OF THE INSANE IN A CHILD,

IN WHICH A GALL STONE WAS FOUND AFTER DEATH.

BY

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ALTHOUGH a considerable number of cases of juvenile general paralysis have now been reported,² it seems worth while to put another on record, as there is still much to be learned about both the diagnosis and the pathology of the disease. The occurrence of a gall stone in a young girl is also a matter of sufficient rarity to merit description.

The patient (I. T.) referred to in the following notes was between 10½ and 11 years of age when she was first recognised as having symptoms of mental disease; and she died at the end of her 17th year.

Family History.—The parents are strong, sober, and apparently healthy people; they are not at all nervous, and both come of unusually healthy and long-lived families. They have had seven children, of whom the patient is the second. The first, third, fifth, and sixth children, who are all alive, have shown distinct signs of congenital syphilis. The fourth child died, when 9 weeks of age, of bronchitis; the seventh is still an infant, and has had no specific symptoms. There have been no miscarriages.

Previous Health.—The mother has no recollection of the patient's having suffered from snuffles or a rash in infancy; but as she made the same statement with regard to a younger child whom I attended for weeks with these symptoms present, her memory is evidently not to be trusted to. When 4½ years old the patient developed a squint, which was operated on nine months later. About the same time she began to suffer from severe and frequent headaches. When 9½ years of age she was brought to the Sick Children's Hospital on account of her headaches, which were especially severe at night. She was found to have extensive patches of choroidal atrophy in both eyes. Her headaches were greatly relieved by iodide of potash. At this time she seemed in other respects a healthy, well-nourished, and intelligent child. She had had no serious illness of any kind, and had never suffered from jaundice nor from any severe dyspeptic disturbances.

Present Illness.—When she was between 10½ and 11 years of age it was observed that she was not improving in her school work, and seemed to be getting stupid and irritable at home. No further change was noted in her mental condition until she was about 12, when fits set in, and she became steadily less intelligent. Her speech was characteristically affected by the time she was 12½ years of age, and her knee-jerks were greatly exaggerated when she was 13 years of age. When about 14 years of age she had several distinct hallucinations. Between 11 and 14 years of age she became unnaturally fat, but afterwards she steadily emaciated. The fits continued at varying intervals during her whole life. Six months before her death she had an attack of subacute periostitis over the right tibia, which was greatly relieved by iodide of potash. She died in a state of extreme debility of mind and body, aged 16 years and 11 months (May 3rd, 1898).

The main clinical features of the case may be summarised as follows:

Appearance, Growth, Etc.—When first seen, the child was well-nourished and of fairly normal size and appearance. Her cranium was well-formed, but the palate was high and saddle-shaped. The upper central incisors were slightly pegged, but they were not typically deformed, and although there was some flattening of the bridge of the nose, and a slight lack of development of the upper jaws, such as is met with in congenital syphilis, there were no facial appearances which could be regarded as pathognomonic of that disease. The main indications of specific disease were the choroidal patches, which were present in both eyes from the beginning of the illness, and the subacute periostitis of the right tibia, which set in shortly before death. Between her eleventh and fourteenth year the child grew very fat, so that she developed a