ON THE SERUM THERAPEUTICS OF CASES OF SNAKE-BITE.

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FOR some time now it has been fully established that an animal which has been treated over a length of time with the venom of a poisonous snake, such as the cobra, yields a serum which is antitoxic towards that poison. It is unnecessary for our present purpose to enter into the many questions of scientific interest which surround this subject; I intend to confine my attention entirely to certain points which must be settled definitely before any method of treatment based on this discovery can hope to take its place among recognised therapeutic measures. The first question, then, which I propose to consider is that of the specificity of antivenomous sera, a question which in this connexion is evidently of the greatest importance. Let us deal with the work on this subject in more or less chronological order. Dr. Calmette of Lille[1] was the first to produce an antivenomous serum in sufficient quantity for therapeutic purposes. This serum was prepared with a mixture of snake venoms, in which mixture, however, cobra poison greatly preponderated. He claimed that this serum was active against the venoms of all species of snakes, a claim based on the conception that all snake venoms are alike in physiological action and only differ from one another in their degree of toxicity. On further experiment this claim was soon seen to be without foundation. Thus it was shown by Martin of Melbourne[2] that Calmette's serum was unable to preserve animals against injections of the poison of the Australian tiger snake (hoplocephalus curtus). Subsequent experiments in Sydney demonstrated a like fact as far as the poisons of other Australian snakes were concerned. In India I[3] conclusively showed that the Lille serum, while active for cobra venom, had no neutralising effect for the poisons of the following snakes: daboia Russellii, bungarus fasciatus, and echis carinata. Dr. F. Tidswell of Sydney[4] next pointed out that Calmette's serum, inasmuch as it was prepared with a mixture of snake venoms, was not strictly adapted for the settlement of the question of specificity, and that it was necessary for this purpose to possess a serum prepared with one single kind of venom and to test its efficacy against the same and other kinds of venom. He therefore immunised a horse with the pure venom of hoplocephalus curtus. With the same end in view I have immunised horses with pure cobra venom. The observations[5] which have been made by Dr. Tidswell and myself with these two sera have already been published in full. A brief summary of the results of these observations, as far as the general actions *in vivo* of the various venoms are concerned, is as follows:—

1. The serum of the horse immunised with hoplocephalus poison was found to be active for the corresponding venom. It completely failed to neutralise the poisons of three other Australian snakes—namely, the brown and black snakes and the death adder. Further, this serum in India was found to be quite inactive against the venoms of the following snakes: cobra, king cobra, bungarus cœruleus (krait), bungarus fasciatus (banded krait), enhydrina valakadien (common sea snake), Russell's viper, echis carinata (phoorsa), trimeresurus gramineus (green pit viper), and crotalus adamanteus (Californian rattlesnake).

2. The serum of a horse immunised with pure cobra venom is strongly antitoxic for the venom used in its preparation; in large quantity it has a slight neutralising power for the venom of enhydrina valakadien; further, it delays death in cases of intoxication with the venom of the king cobra, a species belonging to the same genus as the cobra; it does not, however, completely neutralise this poison, even when used in large quantities. The antitoxic effect against these two venoms is so slight that this serum would be of little or no therapeutic use in cases of bites from these snakes. Finally, this serum has no neutralising action on the venoms of the two colubrine snakes, bungarus cœruleus and bungarus fasciatus, or for the venoms of the following viperine snakes—daboia Russellii, echis carinata, trimeresurus gramineus, and crotalus adamanteus.

It would appear from these observations that the question of specificity was definitely settled. But lately Calmette[6] has made a statement which, however, he does not support by any experimental data. While now admitting that all snake venoms are not alike in physiological action this worker holds that a serum prepared with a venom, such as cobra poison, which is rich in neurotoxic element will neutralise all other venoms which owe their lethal effect to an action on the nervous tissues: in other words, that the neurotoxic elements of all venoms possess the same haptophore groups. In an analogous manner he argues that all viperine venoms which consist principally of "hæmorrhagin" will be neutralised by a serum prepared with a single venom rich in this substance, such as daboia venom. These suppositions of Calmette would appear to receive some support from Rogers's experiments[7] with the serum prepared at Lille. This observer states that this serum neutralised cobra venom well; that when used in large amount it acted next best against the venom of the king cobra and only a little less so in proportion to its toxicity against the venom of enhydrina valakadien. In the case of the krait its action was much more feeble, although still distinct; while in that of the banded krait it prevented all colubrine symptoms. These results, however, were not confirmed by Elliot[8] working in Sir T. R. Fraser's laboratory in Edinburgh. He found that a sample of Calmette's serum which proved definitely antagonistic to cobra venom exerted only a very feeble action against the venom of enhydris curtus and that it was quite powerless to protect animals against ten minimum lethal doses of the venom of bungarus cœruleus. It is to be noted, however, that Rogers used relatively very much larger quantities of serum than did Elliot. It is also to be remembered that all these observations were made with a serum prepared with a mixture of venoms, a serum, as has been pointed out, by no means suitable for the settlement of specificity. However, the results mentioned above, which have been obtained by Tidswell and myself with sera prepared with two pure venoms, show that Calmette's statement requires considerable modification, inasmuch as it was shown that cobra antiserum, when used in large quantity, had only a very slight neutralising effect on the venoms of the king cobra and of enhydrina valakadien and no action at all, if used in a relatively large amount, on the poisons of two species of bungarus, all four colubrine snakes which owe their lethal effects principally, if not entirely, to their actions on the nervous tissues. Analogous results were obtained with the serum prepared with the poison of hoplocephalus curtus, which serum, Tidswell found, had no action on the venom of pseudechis, a poison which Martin[9] has shown has a physiological action absolutely similar to that of hoplocephalus curtus. Further, when we come to test *in vitro* a pure antiserum against the hæmolytic actions of the various poisons we find that specificity is well marked, although not absolute. Thus I have shown[10] that cobra antiserum in this respect has a high neutralising effect for its homologous venom, that it prevents, when used in relatively large amount, this action of the venom of bungarus cœruleus, but that it has no hindering effect at all on the hæmolysing actions of eight other venoms, amongst which was the poison of the king cobra, a species belonging to the same genus as the cobra. Very similar results were obtained with Tidswell's serum, which, however, proved not quite so specific in its action as the serum prepared with cobra venom. Further, both these pure antisera were tested *in vitro* against the actions of the various poisons on the blood coagulability. Without entering into any details of these experiments, I may mention that here also specificity was well marked. Thus cobra antiserum neutralised cobra venom but not king cobra venom, and hoplocephalus antiserum neutralised its homologous poison but not three other poisons which act like it as powerful fibrin ferments.

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[1] Le Venin des Serpents, Paris, 1896. Notice sur le Sérum Antivenimeux et sur le Traitement des Morsures de Serpents, Lille, 1901.
[2] Intercolonial Medical Journal of Australasia, August 20th, 1897. Ibid., April 20th, 1898.
[3] Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India. New series. No. 5, 1903.
[4] Australasian Medical Gazette, April 21st, 1902, p. 177.
[5] Ibid. Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India. New series. No. 5, 1903; No. 10, 1904.
[6] Comptes Rendus de l'Académie des Sciences, 1904, tome cxxxviii., p. 1079.
[7] Proceedings of the Royal Society, vol. lxxii., p. 419; THE LANCET, Feb. 6th, 1904, p. 349.
[8] THE LANCET, July 16th, 1904, pp. 141 and 142.
[9] Royal Society of New South Wales, July 3rd, 1895, Journal of Physiology, vol. xv., No. 4, 1893.
[10] Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India. New series. No. 10, 1904.

In a recent paper Rogers[11] has put on record an extension of his previous observations. Using a serum prepared in London by Messrs. Burroughs and Wellcome with pure cobra venom, he finds that king cobra venom was completely neutralised by this serum. He does not, however, mention the number of lethal doses used or the quantity of serum which was required to effect their neutralisation. He further mentions that with this same serum and the venom of bungarus cœruleus he obtained similar results to those which he had previously obtained with Calmette's serum. Here, again, he does not mention the number of lethal doses used or the amount of serum which was required to effect neutralisation. It would appear, therefore, from all these observations that an antivenomous serum is highly but not strictly specific—a conclusion at which I arrived in my last paper on the specificity of antivenomous sera. In support of this conclusion and of the falseness of Calmette's conceptions are the recent experiments of Noguchi,[12] published as I write. This observer, working with antisera prepared for the venoms of crotalus, mocassin, and cobra, showed that a given dose of anticobra serum protected against five minimum lethal doses of cobra venom when tested on the guinea-pig, against only one of water mocassin venom, and was quite ineffective against crotalus venom; and further, that a given quantity of anticobra serum neutralised two minimal hæmolytic doses of cobra hæmolysin *in vitro* and had no anti-hæmolytic action against crotalus and mocassin hæmolysins, and so on through the remainder of the cross actions. From the results of his experiments Noguchi concludes that the action of antivenenes is highly, if not strictly, specific both *in vivo* and *in vitro*.

The bearing which these results have on the problem of the serum therapeutics of cases of snake-bite is very evident, for at the very outset we are met with the almost insurmountable difficulty that only the specific antiserum must be used in any case of snake-venom intoxication. In this connexion I have already[13] pointed out that for India alone we should require at least six different antivenenes—namely, sera for the venoms of the cobra, the king cobra, the krait, the banded krait, the daboia, and the phoorsa (echis carinata). In the first place, it seems almost impossible to collect these various venoms in quantities sufficient for the purpose of immunisation of large animals. For the last four years arrangements for the collection of venoms, backed by the Government of India and complete in every detail, have been working in the laboratory in Bombay. Even under these most favourable conditions only a very small and quite insufficient amount of these venoms, except cobra and daboia, has been collected. In the second place, granted that it was possible to prepare sera for these different poisons, the practical use of them would be beset with difficulty. For when a person, especially a native of India, is bitten by a snake he is rarely able to tell the species of snake which has inflicted the bite. And, further, as an antivenomous serum to be of much practical utility must be injected before any symptoms of intoxication have set in, the medical man who is called on to treat a case of snake-bite with antitoxin is not as a rule in a position to form an opinion, either from the history of the case or from the symptoms, as to the nature of the venom which has been injected. He would have, therefore, either to use one of the antitoxic sera at haphazard or to inject the whole of them at once, neither of which methods would commend itself as a trustworthy or scientific therapeutic measure.

Having pointed out how the question of the specificity of antivenomous sera influences the practical therapeutics of cases of snake-bite we may now pass to some other and very important points. It has been shown that Calmette's serum has a certain neutralising effect on cobra venom. Further, as I have mentioned above, by using pure cobra venom I have prepared a serum practically specific for this poison. The question, then, of the therapeutic application of these two sera in cases of cobra-bite is at once raised. In this connexion we have first to consider the amount of serum which would have to be injected in order to save the life of a man bitten by this snake. Now a moment's consideration will show that in order to arrive at an accurate therapeutic dose of an antivenomous serum three factors must be determined: (1) the neutralising power of the serum—that is to say, the exact amount of serum which can neutralise a given amount of venom; (2) the amount of poison which the snake has injected; and (3) the quantity of venom the injection of which a man can survive—namely, the maximum non-lethal dose for an ordinary man. It is, of course, apparent that only the first of these factors can be determined with any accuracy. As regards the second it is evident that in treating any case of cobra bite one should always assume that the snake has injected the maximum quantity of venom possible. An estimation of this amount can be arrived at by experiment. The third factor, as we shall see later, is almost negligible. However, an estimation of the probable minimum lethal dose for man may be formed by analogy with that for animals of various species. We shall now consider in detail these three points.

The method of standardisation of the sera which I have adopted in all experiments is based on the conception, now generally acknowledged to be true, that the antagonism between toxin and antitoxin is of the nature of a chemical reaction and is quite independent of vital activity. The sera were tested in every case against ten lethal doses of venom and allowance was made for the amount of poison which the animal could itself deal with. The mixtures of serum and venom were made *in vitro* and allowed to stand at room temperature for half an hour before injection. Working in this way along with Dr. W. Hanna[14] I showed that one cubic centimetre of Calmette's fresh serum was able to neutralise 0·73 milligramme of pure cobra venom. I have now immunised four horses with pure cobra venom, two with unheated poison, and two with venom which had been heated for half an hour at 72° C. These horses have been under treatment for periods varying from three to one and a half years. In each case the serum has been accurately tested at intervals. As with diphtheria toxin immunisation, the results have varied considerably. They have shown that some horses yield a much stronger antitoxin than others, that after reaching a certain strength the serum begins to deteriorate, and that further injections of large amounts of venom have no effect in again increasing its antitoxic power. It is unnecessary for our present purpose to go into the details of these experiments. It is sufficient to note that the serum of highest antitoxic value which I have been able to procure was got from a horse treated for about two years with pure unheated cobra venom. Of this serum one cubic centimetre was able to neutralise 1·5 milligramme of pure cobra venom. As a rule, however, the strength of the different sera was somewhat lower than this. We may take it that an average strength would be one of which one cubic centimetre of serum was able to neutralise about one milligramme of venom, and for practical purposes it seems expedient not to depend on being able to prepare, under the present methods of immunisation, a serum of greater potency than this average. Further, it has to be noted that all my tests were carried out with perfectly fresh sera. Now I have shown[15] along with Dr. Hanna that antivenomous serum undergoes a progressive and fairly rapid deterioration in hot climates, and that this deterioration is greater and more rapid the higher the mean temperature to which the serum is subjected. It is evident, therefore, that the dose of serum would have to be increased in proportion to the time it had been kept and to the temperature to which it had been subjected.

The second factor—namely, the amount of venom which a cobra can inject—is, as I have said, one which can be determined by actual experiment. While Cunningham[16] has estimated this amount on the average at 254 milligrammes, Calmette in his book entitled "Le Venin des Serpents" gives 48 milligrammes as the maximum quantity which he was able to procure from a naja haje of about five feet long. To settle definitely this point I have made three series of experiments. In each series several cobras which had just been captured were weighed and the poison extracted by squeezing the gland secretion into a weighed watch-glass. The poison was then thoroughly dried over lime until a constant weight was obtained. The average amount of dried venom procured from each snake was then calculated. In order to ascertain the effect of captivity on the weight of the snakes and on the amount of venom secreted similar estimations were made at each extraction, which took place at intervals of about a fortnight. After each extraction the

[11] Indian Medical Gazette, September, 1904, p. 332.
[12] Brit. Med. Jour., Sept. 10th, 1904, p. 580.
[13] Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India. New series. No. 5, 1903.
[14] Ibid. No. 1, 1902.
[15] Loc. cit.
[16] Scientific Memoirs by Medical Officers of the Army in India, 1895, Part ix., p. 5.

snakes were fed by means of a funnel passed down into the œsophagus with egg beat up in milk. The following tables show at a glance the results which were obtained.

Experiment I.

Date.	Number of snakes.	Average weight of snakes in grammes.	Average amount of dried venom per snake in grammes.
11.12.01	5	1092	0·240
18.12.01	5	1118	0·108
8.1.02	5	1096	0·180
22.1.02	5	1070	0·187
5.2.02	5	1044	0·253
*19.2.02	4	927	0·133
†5.3.02	3	748	0·080
19.3.02	3	729	0·096
‡2.4.02	2	669	0·080
23.4.02	2	639	0·018
8.5.02	2	697	0·042
22.5.02	2	634	0·031

* Snake, weight 1440 grammes, had died. † Snake, weight 1459 grammes, had died. ‡ Snake, weight 870 grammes, had died.

Experiment II.

Date.	Number of snakes.	Average weight of snakes in grammes.	Average amount of dried venom per snake in grammes.
13.12 01	3	791	0·182
20.12.01	3	808	0·184
8.1.02	3	743	0·238
22.1.02	3	726	0·249
*5.2.02	2	650	0·259
19.2.02	2	672	—
5.3.02	2	655	0·239
19.3.02	2	710	0·254
2.4.02	2	680	0·181
23.4.02	2	680	0·052
8.5.02	2	695	0·051
22.5.02	2	680	0·045

* Snake, weight 835 grammes, had died.

Experiment III.

Date.	Number of snakes.	Average weight of snakes in grammes.	Average amount of dried venom per snake in grammes.
16.12 01	6	585	0·248
23 12.01	6	588	0·109
9.1.02	6	592	0·203
23.1.02	6	586	0·167
6.2.02	6	544	0·147
*20.2.02	5	537	0·098
†6.3.02	4	503	0·114
20.3.02	4	483	0·048
‡3.4.02	3	465	0·039
§24.4.02	1	495	0·119
8.5.02	1	415	0·047

* Snake, weight 495 grammes, had died. † Snake, weight 720 grammes, had died. ‡ Snake, weight 450 grammes, had died. § Two snakes, weight 520 and 380 grammes, had died.

From these tables it is seen that when cobras are kept in captivity and the poison extracted regularly there is an almost progressive loss of weight and also an almost progressive diminution in the amount of poison secreted. This latter fact no doubt explains the low estimate which Calmette has made of the amount of venom which a snake can inject. In the experiments collated above the poison was squeezed out by firm pressure with the finger and thumb over the glands. Inasmuch as in nature no such artificial assistance is given to the ejection of the venom an objection might be brought against these estimations. When, however, we consider the perfect mechanism by means of which a cobra naturally empties its poison glands the question at once suggests itself as to whether squeezing the glands really yields as much poison as the snake can itself eject. This point was put to practical experiment. Three fresh full-grown cobras, of an average weight of 1228 grammes, were allowed to bite through a sheet of rubber stretched over a weighed watch-glass. The amount of dried venom got in this way was then determined. A total quantity of 1·12 grammes was obtained—that is, an average of 373 milligrammes from each snake, an amount considerably greater than that got in any of the three experiments detailed above. For our present purpose these observations may be summed up as follows: from 14 fresh cobras of good size an average amount of 231 milligrammes of dried venom per snake was got by squeezing the glands; from three fresh cobras an average amount of 373 milligrammes was obtained by allowing the snake to bite. Rogers[17] has recently confirmed these experiments, which were done nearly three years ago. He found that the average amount of dried poison got from two full-sized cobras was 249 milligrammes. It is quite evident, then, from these observations that in estimating the dose of antivenomous serum to be used in the treatment of any case of cobra bite one should always have in mind the fact that the snake may have injected as much as from 250 to 350 milligrammes of poison, for the neutralisation of which quantity sufficient serum would have to be injected if one wished to save the life of the patient. There must be, of course, many cases in which less, probably a good deal less, venom would be injected and in such cases a smaller amount of serum would suffice. But the difficulty arises in there being no means by which one could judge of this and as treatment must be immediate there is no time to wait and watch the development of the case.

We have now to consider briefly the third factor which bears on the determination of a therapeutic dose of anti-cobra serum in a case of cobra bite. Fraser[18] has estimated that the minimum lethal dose of cobra venom for an average man would be about 31 milligrammes, while Calmette's[19] estimation is 10 milligrammes. I have now accurately determined the minimum lethal dose of this poison for animals of different species and of different sizes. The results are contained in the following table.

Minimum Lethal Dose of Dried Cobra Venom per kilogramme of weight in milligrammes.

—	Rat.	Rabbit.	Dog.	Monkey.	Horse.
Cobra venom in milligrammes	0·33	0·35	0·5	0·25	0·09

From this table it is seen that the horse, weight for weight, is the most susceptible of the animals experimented with and the monkey the next most susceptible. If, then, the susceptibility of man be at all analogous to that of the monkey we can calculate that the minimum lethal dose for a man of from 60 to 70 kilogrammes weight would be from 15 to 17·5 milligrammes, an estimate between those of Calmette and Fraser. We may therefore take it that a man would probably be able to survive about 15 milligrammes of cobra venom, an amount almost negligible if the snake had injected the maximum amount of poison possible.

Having as far as is possible experimentally determined the three factors on which the dose of serum to be used in any case of cobra bite rests we have now only to calculate what this dose would be. In a previous communication[20] along with Dr. Hanna, using the data at that time available, I recommended that in every case of cobra bite from 30 to 35 cubic centimetres of Calmette's serum should be given and a larger quantity if symptoms had already set in. This estimation was founded on the assumption that the maximum amount of venom which a cobra could inject was about 45 milligrammes, a figure taken, as we have seen, from Calmette's observations. In view, however, of the facts brought forward above it is evident

[17] Indian Medical Gazette, September, 1904, p. 332.
[18] Brit. Med. Jour., April 18th, 1896, p. 957.
[19] Loc. cit. [20] Loc. cit.

that this estimation will require considerable amendment. If, then, the serum be of ordinary strength—namely, that one cubic centimetre is able to neutralise one milligramme of pure unheated cobra venom—and if the snake had injected the maximum amount of poison possible—namely, about 350 milligrammes—we can calculate that in order to neutralise this amount of venom and thus save the life of the patient 350 cubic centimetres of serum would have to be brought in contact with it. If the serum were not of the strength mentioned above or if it had deteriorated through keeping a larger quantity would be required. We have still to consider the method of injection, as this amount of serum is the quantity which would be required to neutralise completely 350 milligrammes of poison when they are mixed *in vitro* before injection. Martin,[21] repeating and extending some experiments by Fraser, has found that if a quantity of venom subcutaneously, and a neutralising dose of antivenine intravenously, be injected at the same time into an animal as good results are obtained as when the venom and serum are mixed *in vitro* before injection. If, however, the serum be injected subcutaneously at the same time as the venom, then it was found that from 10 to 20 times the neutralising dose of serum was required to save the life of the animal. Applying these observations to our present purpose we arrive at the conclusion that in treating a case of cobra bite in which the snake had injected the maximum amount of poison we should have to inject 350 cubic centimetres of serum intravenously or from 3500 to 7000 cubic centimetres subcutaneously in order to save the life of the patient. Further, if symptoms have already appeared before treatment was begun larger amounts of serum would be required to dissociate the poison from its junction with the nerve cells. There are, of course, many cases of cobra bite, cases in which the snake from many reasons may not have injected the full amount of poison possible, for the treatment of which a much smaller quantity of serum would suffice. But, as I have said, in treating any case of cobra bite we must always start with the assumption that the snake may have injected as much as 370 milligrammes of poison. We have, therefore, other difficulties to contend with in the serum therapeutics of cobra bite. The serum must be given intravenously and even then in very large quantity, too large in many cases to bring this method of treatment within the bounds of practical therapeutics. This estimation of the amount of serum which would have to be used in cases of cobra bite has received support from some experiments made on dogs by Major P. Carr-White, I.M.S.[22] This observer allowed cobras to bite dogs, treating them with anti-cobra serum immediately after the bite, and in one case even before the bite. The amount of serum injected varied from seven cubic centimetres to 60 cubic centimetres. The injections were all made subcutaneously. In all seven dogs were thus experimented with and in no case was the life of the animal saved, nor was the least benefit from the use of the antivenine noticed when these animals were compared with two controls which received no serum. An animal which received 60 cubic centimetres of perfectly fresh serum died in the same time as the controls, although the serum was injected before any symptoms of cobra poisoning had set in. It is evident, then, that in these experiments the snakes had injected a considerable amount of venom and that the quantities of serum used, although injected under the best possible conditions, were much too small to effect complete neutralisation.

Finally, I have now to draw attention to the results which have been obtained in India by the use of antivenomous serum during the years 1900–03. Through the kindness of the sanitary commissioner with the Government of India I have had access to the reports of all cases of snake-bite treated with serum during this period. In the great majority of these cases the snake was not identified. But I have already pointed out that both Calmette's serum and the serum prepared at this institute with pure cobra venom, the only two sera which have been in use, are practically specific and that no advantage would result from their injection in cases other than cobra bite. We have therefore to consider in detail only those cases in which the snake was killed and identified as a cobra. In all, 11 cases of undoubted cobra bite were treated; of these, eight recovered and three proved fatal. The details of the eight cases which recovered are as follows.

1. *Case which occurred in the Bombay Laboratory, reported in* THE LANCET *of Jan. 5th, 1901, p. 25.*—In this instance the snake had been in captivity for some months, during which period the poison had been extracted at regular intervals. Further, only one fang penetrated the skin. It is evident, therefore, that only a very small amount of venom can have been injected and that the quantity of serum used—namely, 28 cubic centimetres—was sufficient to neutralise this.

2, *Case reported by Colonel Scott-Reid, I.M.S., in the "Indian Medical Gazette" of October, 1901.*—While removing some pigeons from a cot in which the snake was concealed a man was bitten on the forefinger by a cobra three and a quarter feet long. The snake, however, had recently killed five pigeons, one of which was found in its stomach and four on the ground beneath the cot. A ligature was at once applied round the finger and 10 cubic centimetres of serum were injected subcutaneously. No constitutional symptoms of cobra poisoning were observed. It is probable that in this case the snake had partially or completely exhausted its venom on the pigeons before the man was bitten.

3. *Bareilly case reported by Major P. C. H. Gordon, R.A.M.C.*—A native was bitten by a cobra three feet long. Two small punctures were found on the dorsum of the right second toe. A tight ligature was immediately applied round the ankle. On arrival at hospital one hour after the bite two incisions were made over the site of the punctures and the wounds washed with chloride of lime (1 in 60); ten cubic centimetres of Calmette's antivenine were injected subcutaneously. No symptoms of cobra venom intoxication developed.

4. *Khandalla case, reported by Captain H. A. L. Howell, R.A.M.C.*—A soldier was bitten on the forefinger by a cobra three and a half feet long, which was a pet belonging to one of his comrades. A tight ligature was immediately applied round the forearm and ten cubic centimetres of Calmette's serum were injected half an hour after the bite. No symptoms of cobra poisoning developed. In this case it is probable that as the snake was a pet the glands had been removed or destroyed before it was purchased, a procedure common among snake men in India.

The following four cases are taken from the annual sanitary reports of the administrative medical officer, Central Provinces.

5. In this case the cobra was a young one, the bite was imperfect, one fang only having penetrated, and the antivenine was injected between five and six hours after the bite, up to which time no symptoms had developed.

6. A middle-aged man was bitten by a cobra three and a quarter feet long. One puncture only was seen and when the snake was examined by the civil surgeon it was found to have only one fang. Four hours later, symptoms of poisoning being then present, 30 cubic centimetres of antivenine were injected subcutaneously; nearly an hour later 30 cubic centimetres more antivenine were injected. Improvement soon followed and a complete recovery was made.

7. A man, aged 24 years, was bitten on the hand; one fang went home but the second evidently slipped between the two fingers, inflicting only a graze. 40 cubic centimetres of antivenine were injected about 50 minutes after the infliction of the bite. Up to that time no prominent symptoms of poisoning had developed nor did any appear subsequently. The snake was killed and found to be a cobra four and a half feet long.

8. The patient was bitten on the foot; 20 cubic centimetres of antivenine were injected within from ten to 15 minutes; no definite symptoms had appeared prior to injection, nor did any appear subsequently. The snake was killed and identified by the hospital assistant as a young cobra.

It is evident from a perusal of these cases that in no instance did the snake inject anything like the maximum amount of venom possible. To this fact are no doubt due the successful results of the treatment. The details of the three fatal cases are as follows.

9. *Case reported by Administrative Medical Officer, Central Provinces.*—A man was bitten on the hand by a cobra, two and a half feet long. Within an hour and before definite symptoms of poisoning had appeared 30 cubic centimetres of Calmette's antivenine were injected subcutaneously. About 15 minutes later the symptoms of poisoning became marked. Ten cubic centimetres more antivenine were then injected. The man died an hour later.

[21] Brit. Med. Jour., Sept. 10th, 1904, p. 577.
[22] Indian Medical Gazette, November, 1902, p. 431.

10. *Dehra Doon case, reported by Lieutenant-Colonel F. W. Wright, I.M.S.*—A man was bitten on the back of the left hand by a cobra, two and a half feet long. A tight ligature was at once applied round the wrist. The injection of antivenine began an hour after the bite and before any symptoms of poisoning had set in. In all 55 cubic centimetres of serum were given, ten cubic centimetres being injected intravenously and 45 cubic centimetres subcutaneously. The man died three and a half hours after the bite.

11. *Bareilly case reported by Captain L. P. More, R.A.M.C.*—A boy was bitten on the left thumb by a cobra a little over three feet long. A ligature was at once applied tightly round the wrist. Three-quarters of an hour after the bite the wounds were incised and crystals of permanganate of potassium rubbed in; 55 cubic centimetres of antivenomous serum were then injected, ten cubic centimetres intravenously and 45 cubic centimetres subcutaneously. The patient died two and a half hours after the bite.

In these three cases, all authentic cases of cobra bite, the serum treatment completely failed. As in the experiments on dogs, the injection of the serum seemed to have no effect whatever on the progress of the case. In each instance the patient came under treatment within an hour after being bitten, a large quantity of serum was injected, and in one case vigorous local treatment, as recommended by Fayrer, Brunton, and Rogers,[23] was resorted to. It is evident that in these cases the snake got a proper bite, that a considerable quantity of venom must have been injected, and that the amount of serum used was quite insufficient to neutralise this.

The following conclusions may now be drawn.

1. Antivenomous sera are markedly if not absolutely specific, even between the venoms of species of the same genus. Hence in any case of snake-bite the serum prepared with the venom of that species which has inflicted the bite must always be used.

2. The difficulties in collecting the poisons of the different species of snakes in sufficient quantity for purposes of immunisation are apparently very great.

3. Up to the present the only sera which have been used practically are the one prepared by Calmette and the one prepared at this institute with pure cobra venom. Both these sera are practically specific for cobra venom.

4. As the neutralising power of these two sera is not great and as a cobra can inject a large amount of venom the serum must be given in large quantity; as much as from 300 to 400 cubic centimetres, even when given intravenously, would be necessary in some cases. If given subcutaneously from ten to 20 times this amount would be required. It should therefore always be given intravenously.

5. Experiments on dogs and the records of cases of cobra bite in man bear out these calculations.

6. It is evident from the above considerations that it is a question as to whether the advantages to be gained by the serum treatment of cases of snake-bite are at all commensurate with the cost entailed in the preparation of the sera.

Note.—Just as this paper was being despatched the number of the *British Medical Journal* of Sept. 10th, 1904, containing the paper by Dr. C. J. Martin, read before the pathological section of the British Medical Association, arrived. On the subject of the specificity of antivenomous sera Dr. Martin arrives at practically the same conclusions as I have put forward in this paper.

Kasauli, India.

A REMARKABLE SEQUEL TO A CASE OF GASTRO-ENTEROSTOMY.

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THE after-history of cases of gastro-enterostomy is always a matter of great interest and will some day be an important chapter in the consideration of the procedure. In the meanwhile it behoves those of us who are constantly doing this operation for one condition or another to watch the subsequent history of our cases closely over long periods and to record any unusual sequel which has been observed. The following case is offered as a contribution in this direction and possesses much intrinsic interest besides. It appears so far to be unique but it is possible that its publication may bring to light similar or analogous cases of the existence of which I at least am unaware.

The patient, a woman, aged 28 years, was admitted into University College Hospital two years ago for severe recurrent hæmorrhage from the stomach. As this had resisted all medical treatment I was asked to deal with it surgically. I accordingly performed a posterior retrocolic gastro-enterostomy in the usual way and recovery followed perfectly and with complete relief in due time of the hæmatemesis. The patient's health became excellent and she was married on March 21st, 1904. Pregnancy soon followed and is now (August) nearly five months advanced. About a month ago she began to have attacks of pain, most frequent after food and referred to the region underlying the scar just above the umbilicus. On July 21st the pains became worse and the patient had to remain in bed the whole day. The bowels acted normally on the 20th but not since. Vomiting began on the 21st. On the 23rd she vomited three times, mostly bilious matter according to her own account, and on the 24th again three times, also green. On this day she was re-admitted into hospital at 6 P.M. The following notes of her condition were made by the surgical registrar.

The patient is fairly well nourished but pale and looking ill. The abdomen moves slightly on respiration and is a little distended, partly due to four months pregnancy. The patient lies on her back with the legs drawn up. Pulse 99, good quality, respiration normal. The abdomen is slightly tender all over, but excessively so above the umbilicus in the median line. The muscles are not very rigid. Rectal examination reveals an enlarged uterus corresponding to the fourth month of pregnancy, otherwise negative. There is no movement of intestinal coils to be seen. There was no evidence of general peritonitis.

When I saw the patient at 7.30 P.M. she was as above described but was writhing with pain. I regarded the cause as probably intestinal obstruction due to an adhesion about the scar and proceeded at once to operate. Under chloroform an incision was made in the middle line *below* the umbilicus. Slipping the finger in under the scar not a trace of adhesion to it could be found. The wound was then enlarged upwards through the old scar which was perfectly firm. Some free ascitic fluid now ran out and dark, distended coils of small intestine presented on both sides. The transverse colon was sought for and drawn out and was found to be pale and much contracted. Search was then made for the gastro-enterostomy junction but it could not be clearly made out. With the finger I could feel the plica duodeno-jejunalis at the root of the left side of the mesocolon but the direction of the first part of the jejunum was not clear. On the right side of the middle of the mesocolon small intestine was felt passing under some tightly constricting mass and on drawing the coils aside the last seven or eight inches of the ileum (I), tense and contracted to the size of the little finger, were seen ending in the normal cæcum and twisted on its own axis. Following this back it was seen to pass behind the gastro-enterostomy junction and to be twisted on itself at the point of constriction. It was now plain to all present that the whole of the small intestine with the exception of the last seven inches or so had passed between the junction of the stomach and jejunum and the root of the mesocolon made two years ago and over the first part of the jejunum (A) (afferent) and then down into the general cavity of the peritoneum. But not only this, the whole small intestine having thus passed formed a huge volvulus, turning on its mesentery in a direction contrary to the movements of a clock. When this was recognised the coils as a whole were lifted up and untwisted one complete turn in the direction of the movements of the hands of a clock. Only then could the last part of the ileum (I) be withdrawn from under the constriction, all previous efforts in this direction having failed. But when the volvulus was untwisted it and all the rest of the small intestine above it could be easily and rapidly drawn out. The junction with the stomach could now be plainly seen and both the afferent and efferent limbs going to and from it. It was placed in the normal position, the coils were washed with normal saline solution (warm), and the abdomen was closed. The operation lasted 65 minutes and was well borne. Convalescence was uninterrupted and primary union was found when the stitches were removed on the eighth day.

Immediately after the operation the patient vomited for

[23] Proceedings of the Royal Society, 1904, vol. lxxiii., No. 494, p. 323.