

## INTRAVASCULAR ANTISEPSIS.

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THE idea that drugs might advantageously be administered by direct injection into the circulation was first started by an English mathematician and architect and has had its latest exponent in an Italian Cabinet Minister. Sir Christopher Wren in 1656 was the first to carry out the "noble anatomical experiment" and the medical profession has coquetted with the method ever since—exaggerated enthusiasm for it alternating with absolute neglect. Ettmüller, Purmann, Major, and Escholtz during the last half of the seventeenth century, and Percy, Majendie, Scheel, and Dieffenbach during the first quarter of the nineteenth century gave the method extended trials. Since the latter period, Oré and Halford endeavoured to introduce it for special purposes but met with no lasting success; whilst recently Baccelli, Landerer, Maguire, and others have revived it in connexion mainly with the treatment of bacterial diseases or diseases presumably of parasitic origin. That it is possible to introduce small quantities of a large number of substances directly into the veins cannot be denied but that any great advantage can be obtained by such a procedure has never as yet been experimentally demonstrated. The advocates of the "Chirurgia Infusoria," as Major called it, have based their opinions as to its merits on various grounds, and it is only with the attempts to carry out one of the recent theories for its application that the present paper will deal. For many years experimenters and clinicians have been endeavouring to apply antiseptic principles to the treatment of septicæmic diseases. Baccelli, who introduced the intravenous injection of perchloride of mercury in syphilis (a proceeding which, after prolonged trial throughout Europe, has been practically abandoned as presenting no special advantages), extended his method to epidemic cerebro-spinal meningitis, acute rheumatism, and other diseases, notably aphtha epizootica in cattle. His early successes with the last-mentioned ailment have not, however, been attained by other observers; in fact, it has been conclusively shown that perchloride of mercury injected intravenously has absolutely no effect either in preventing or modifying an attack.<sup>1</sup> The effect was undoubtedly intended to be that of an internal antiseptic but a dilution strong enough to harm any bacteria living in the blood could not be obtained with a non-toxic dose of the drug. Maguire and Ewart<sup>2</sup> in this country have recently tried to render the lungs aseptic by injecting comparatively large quantities of formic aldehyde and protargol respectively. 200 tuberculous patients have been treated by the former method and the results, except in severe cases, are reported as successful. A solution of formic aldehyde (1 in 100,000 in the blood) can be passed through the lungs for half an hour, while Ewart has succeeded in flushing the smaller circulation with protargol of a strength equal to nearly 1 in 500. Of these two methods only the latter can be said *primâ facie* to have any chance of success, the formic aldehyde solution being too weak to exert any effect *in vitro*. The clinical evidence, however, is, according to both experimenters, encouraging. Credé<sup>3</sup> in Dresden has injected a preparation of citrate of silver, but the exact antiseptic power of the solution *in vitro* has not been accurately determined, so far as I am aware, and the clinical results are too few in number and too miscellaneous in character to carry much weight.

As against these clinical experiments there is a growing mass of laboratory work which may be said to be wholly unfavourable to the idea of intravascular antiseptics. In 1887 Behring<sup>4</sup> found that oxide of silver when injected in non-lethal doses into rabbits, guinea-pigs, and mice infected with anthrax rather lengthened the life of the animals. In toxic

doses the anthrax bacilli were only rarely found post mortem in the blood and organs.

The late Dr. J. W. Washbourn<sup>5</sup> in 1888 injected creolin subcutaneously, but failed to cure either rabbits or mice, though fewer anthrax bacilli were found in the animals treated. Fischer and Fricker<sup>6</sup> tried intra-peritoneal injections of formic aldehyde in guinea-pigs inoculated with tubercle, but found that in all cases the control animals survived those which had received the injections. In 1884 Cash<sup>7</sup> succeeded in curing rabbits of anthrax by hypodermic injections of perchloride of mercury. The injections were made for some weeks before inoculation and were not by any means uniformly successful. Koch<sup>8</sup> and Behring,<sup>9</sup> who repeated his experiments, failed to get positive results, and Cadéac<sup>10</sup> stated that dogs treated in this way actually had their resistance to anthrax considerably diminished. During the past year Spissu<sup>11</sup> and Serafini<sup>12</sup> made some accurate and extensive investigations with the same drug. The former observer determined the maximum non-lethal dose for rabbits at 0.0003 gramme per 100 grammes body-weight, but found that even toxic doses failed to prevent the growth of anthrax bacilli in the blood. Serafini's dosage was 0.00027 gramme per 100 grammes body-weight and he also had negative results both with anthrax and fowl cholera in rabbits. With a view of obtaining further evidence on this subject the following experiments were carried out at the Jenner Institute of Preventive Medicine during the summer of the past year. In planning these experiments I had two objects in view; firstly, to test the toxicity of various antiseptics when injected into the veins of rabbits, and secondly, to discover if any of them exerted an influence on the course of an artificially produced septicæmia. The actual injections were kindly made for me by Dr. A. Macfadyen.

The following substances were chosen for the first series of experiments: (1) perchloride of mercury, (2) oxycyanide of mercury, (3) formic aldehyde, (4) chinosol, (5) a mixture of formic aldehyde and chinosol, (6) protargol, and (7) taurocholate of sodium. In all cases the solutions were freshly prepared for each injection, the substances being carefully weighed on a chemical balance; the injections were made with antiseptic precautions into the marginal veins in the rabbit's ears. The idea was so to regulate the doses that a number of injections could be made on successive days, not merely one large injection at a given time after infection, as was the case in Spissu's and Serafini's experiments. In this way I thought it possible that some tolerance of the drugs might be established.

1. Five rabbits were treated with perchloride of mercury in various strengths, but even in dilutions of 1 in 2000 doses of half a cubic centimetre repeated at intervals of about 48 hours produced progressive emaciation, while larger doses (six cubic centimetres of 1 in 1000) repeated daily for three days gave rise to diarrhoea and death. In the former case the proportion of perchloride of mercury was 0.00001 gramme per 100 grammes body-weight, which would approximate to 0.00013 per cent. solution of the salt in the total volume of the blood; 1 in 2000 perchloride of mercury being necessary to kill anthrax bacilli in blood serum (Behring<sup>13</sup>) no further experiments were made with this substance.

2. Rabbits were found to tolerate oxycyanide of mercury ( $\text{HgOHg}(\text{CN})_2$ ) in a proportion of 0.00004 to 0.00005 gramme per 100 grammes body-weight, which would produce a solution of about 0.0006 per cent. to 0.0007 per cent. in the blood. De la Croix<sup>14</sup> found that 0.00125 per cent. was necessary to inhibit the growth of anthrax in broth. Larger doses, however, were not found practicable as the animals rapidly lost weight and died.

3. Formic aldehyde in 1 per cent. solution can be injected with safety in small doses. Two cubic centimetres of a 1 in 65 solution produced in one rabbit an immediate discharge of mucus from the nose, and with solutions of this

<sup>5</sup> Guy's Hospital Reports, 1888, p. 365.

<sup>6</sup> Transactions of the Chicago Pathological Society, Feb. 10th, 1902, p. 61.

<sup>7</sup> Local Government Board Medical Officer's Report, 1884, p. 200; 1885, p. 185.

<sup>8</sup> Mittheilungen aus dem Kaiserlichen Gesundheitsamte, 1881, Band i., p. 280.

<sup>9</sup> Bekämpfung der Infektions-Krankheiten, 1894, p. 35.

<sup>10</sup> Journal de Physiologie et Pathologie Générales, tome iv., p. 121, 1902.

<sup>11</sup> Riforma Medica, Fasc. 84, p. 99, 1902.

<sup>12</sup> Münchener Medicinische Wochenschrift, Band xl., p. 649, 1902.

<sup>13</sup> Flügge: Die Mikro-organismen, Band i., p. 452, third edition, 1896.

<sup>14</sup> Archiv für Experimentelle Pathologie und Pharmacologie, Band xiii., p. 175, 1881.

<sup>1</sup> Journal of Comparative Pathology and Therapeutics, 1902, p. 87.

<sup>2</sup> Proceedings of the British Congress on Tuberculosis, 1901, vol. iii., pp. 438 et seq.

<sup>3</sup> Berliner Klinische Wochenschrift, Band xxxviii., 1901, p. 941.

<sup>4</sup> Deutsche Medicinische Wochenschrift, Band xiii., p. 830, Sept. 22nd, 1887.

strength some irritation of the nasal mucous membrane generally occurred, as evidenced by the animal standing up on its hind legs and rubbing its nose with the fore paws for some little time. A 2 per cent. solution generally led to œdema of the ears after a few days. One cubic centimetre of a 1 per cent. solution injected about every other day, representing a proportion of about 0·00045 gramme per 100 grammes body-weight, led to progressive emaciation when prolonged for more than a fortnight, 200 grammes being lost in nine days. Doses of this strength would amount to about 0·006 per cent. formic aldehyde in the blood; 0·002 per cent. solutions in broth have a noticeably inhibitory action on bacillus anthracis (Flügge).

4. Chinosol ( $C_9H_8NKS O_4$ ) in doses of 0·002 gramme per 100 grammes body-weight almost invariably produced transitory paralysis; 0·0004 gramme to 0·0005 gramme per 100 grammes body weight could be given about every other day for ten days without adverse symptoms, but the weight then fell progressively, although the injections were suspended. This dose amounts to a solution of from 0·005 per cent. to 0·006 per cent. in the blood; the former strength has been found by Benecke<sup>15</sup> to produce an antiseptic effect on anthrax bacilli in nutrient media after an exposure of 24 hours.

5. The mixture of formic aldehyde and chinosol was given in 0·5 cubic centimetre doses, each drug being represented in a proportion of 0·00028 gramme per 100 grammes body-weight. The toxic effects (loss of weight and general symptoms of malaise) were, however, so marked even after two or three injections that no further experiments were made.

6. Protargol in doses of from 0·0002 gramme to 0·0003 gramme per 100 grammes body-weight every second or third day produced steady loss of weight from the beginning. Larger doses occasionally produced paralysis. This represents about 0·004 per cent. solution in the blood. Benario<sup>16</sup> states that a 0·01 per cent. solution of protargol has no inhibitory effect *in vitro*.

7. Sodium taurocholate is the most active antiseptic of the substances found in bile. It is, however, very toxic when injected intravenously in rabbits, 0·00005 gramme per 100 grammes body-weight injected every other day producing progressive emaciation after five days. The solution in the blood was 0·0007 per cent. The exact antiseptic power of this substance has not, so far as I know, been accurately determined.

The conclusions drawn from this series of experiments are:—1. That perchloride of mercury, oxycyanide of mercury, and protargol cannot be injected intravenously into rabbits in sufficient strength to produce an antiseptic effect lasting over several days. 2. That a mixture of chinosol and formic aldehyde is too toxic even in minute doses to be of use for practical purposes. 3. That chinosol or formic aldehyde can be injected intravenously so as to produce a solution which would have an inhibitory action *in vitro*. 4. That sodium taurocholate can be injected in small doses but that toxic effects manifest themselves after a few days.

In the second series of experiments the effects of injections of the above substances on infected animals were investigated. Perchloride of mercury, however, was not tried, as former observers have reported very unfavourably on its action. Owing to its toxicity the mixture of chinosol and formic aldehyde was likewise omitted. The anthrax for inoculation was prepared as follows. The blood of a guinea-pig recently dead from the disease was planted on an agar tube and incubated for 24 hours at 37°C. The purity of the cultivation having been established by microscopical examination a small platinum loop holding about 0·3 milligramme was filled with the growth and transferred to 10 cubic centimetres of broth for 16 hours at 37°C. No spores were detected in this growth. Six rabbits were then inoculated intraperitoneally with 0·5 cubic centimetre of the cultivation, which had been diluted with an equal volume of sterile broth and well shaken up so as to form a homogeneous emulsion. The drugs selected were then injected into five of the rabbits in the following proportions: oxycyanide of mercury, 0·00005 gramme per 100 grammes body-weight; formic aldehyde, 0·0007 gramme per 100 grammes body-weight; chinosol, 0·001 gramme per 100 grammes body-weight; protargol, 0·0004 gramme per 100

grammes body-weight; and sodium taurocholate, 0·00006 gramme per 100 grammes body-weight. These injections were repeated every 24 hours, those of chinosol and protargol, however, being reduced to one-half the original proportion after the first dose. The oxycyanide, formic aldehyde, and chinosol rabbits were found dead on the fifth day. The rest, including the control animal, survived. Post-mortem examination, which included opening the thorax and abdomen under full aseptic precautions and the making of cover-slip preparations and agar cultivations from the blood of the heart and spleen, showed that all the animals died from anthrax septicæmia. The three remaining rabbits on the eighth day after the first inoculation were re-inoculated with a dose of anthrax prepared in the same way as the first, only of twice the strength, the broth cultivation not being diluted. Protargol and taurocholate of sodium were injected in the same proportions as before. The taurocholate rabbit lived three days, the control rabbit four days, and the protargol rabbit four and a half days after the second injection. The post-mortem methods and results were the same as in the first three cases.

Another series of six rabbits was then inoculated with the stronger dose of anthrax emulsion in the same manner as on former occasions. Five of them were injected daily in the following proportions: oxycyanide of mercury, 0·00005 gramme per 100 grammes body-weight; formic aldehyde, 0·001 gramme per 100 grammes body-weight; chinosol, 0·0005 gramme per 100 grammes body-weight; protargol, 0·0003 gramme per 100 grammes body-weight; and sodium taurocholate, 0·00005 gramme per 100 grammes body-weight. The injections were repeated daily till the death of the animals, which occurred in the following order: oxycyanide of mercury and sodium taurocholate, died after two and a half days; protargol, died after three days; formic aldehyde and control died after three and a half days; and chinosol, died after four days. Post-mortem results showed that all animals died from anthrax. In no case was there any evidence of an inhibitory action on the part of the antiseptic.

As in the case of formic aldehyde and chinosol a sufficient dose could be administered to obtain what *in vitro* would be an antiseptic action, a further experiment was tried with these substances, the organism chosen being the pneumococcus owing to its more feeble resistance to bactericides. This organism was grown from a virulent strain on standardised blood-agar tubes, one loopful (0·3 milligramme) being diluted 100,000 times in sterile broth and 1 cubic centimetre of the emulsion injected subcutaneously. The dose, therefore, was 0·00001 loopful. The proportion of the antiseptics injected was: formic aldehyde, 0·0021 gramme per 100 grammes body-weight; chinosol, 0·003 gramme per 100 grammes body-weight; and the dose administered three times during the first day. On the second day two doses were given of formic aldehyde, 0·0025 gramme per 100 grammes body-weight, and chinosol, 0·0035 gramme per 100 grammes body-weight. On the third day the formic aldehyde rabbit received 0·0029 gramme per 100 grammes body-weight twice and the chinosol rabbit 0·0044 gramme, the latter animal dying a few hours later. The former animal died during the next 24 hours. The control died on the sixth day. Paralysis was observed after each chinosol injection. The post-mortem results were positive.

From these experiments the following conclusions may be drawn: (1) that rabbits injected daily with non-toxic doses of oxycyanide of mercury, formic aldehyde, chinosol, protargol, or taurocholate of sodium are not thereby protected from the usual effects of a previous inoculation of virulent anthrax; and (2) that chinosol and formic aldehyde in large doses (toxic) so depress rabbits infected with the pneumococcus that they die sooner than an untreated animal.

Generally, then, it may be said that at present there is no experimental evidence which would warrant the assumption that the course of a septicæmia in animals can be influenced favourably by the intravenous injection of antiseptic substances, and that the only result to be obtained by pressing such a treatment beyond the maximum non-toxic dose is to hasten the death of the animal. In view of the results described in this paper and those obtained by former investigators it seems useless to continue trying to apply clinically a method which, while by no means free from special dangers and difficulties, is at present unsupported by any experimental evidence either as to its present advantages or future prospects.

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<sup>15</sup> Centralblatt für Bacteriologie Zweite Abtheilung, 1897, Band iii., p. 65.

<sup>16</sup> Deutsche Medicinische Wochenschrift, Band xxiii., p. 82, T. 1897.