

## SOME EXPERIMENTS ON THE INTRAVASCULAR USE OF ANTISEPTICS.

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THE prominence given to the intravascular use of antiseptics has hardly been in accord with the results achieved by this method.

The injection of formalin in various amounts and strengths has been given an extended trial in the treatment of pulmonary tuberculosis, and is claimed to have produced beneficial results<sup>1</sup>. Similarly Baccelli has injected corrosive sublimate intravenously in the treatment of syphilis, cerebro-spinal meningitis, and acute rheumatism in man. In animals he has used intravenous injections of corrosive sublimate in the treatment of aphtha epizootica. In this disease he claims that the intravenous injections of corrosive sublimate are of undoubted use in terminating an attack of the disease<sup>2</sup>.

Further, Baccelli states, "It is finally a hygienic measure, preservative, as it destroys *in situ* the source of infection<sup>3</sup>." That is, he claims that antiseptics act as such when injected intravenously. But in the above instances other methods of treatment have been simultaneously applied and the cure, if any, might not have been due to the antiseptic part of the treatment.

Ewart has reported favourably on the intravascular injection of protargol in cases of tuberculosis; and Behring, in 1887, thought that silver oxide had a favourable effect on the course of experimentally produced anthrax in animals. Cash has also obtained positive results with corrosive sublimate<sup>4</sup>.

<sup>1</sup> *Proc. Brit. Congr. Tuberculosis*, 1901, Vol. III. p. 438.

<sup>2</sup> *Lancet*, Jan. 3, 1903.

<sup>3</sup> *Boll. Chem. Farmaceut.* Feb. 1902.

<sup>4</sup> *L. G. B. Med. Off. Reports*, 1884 and 1885.

Against these we have the evidence of Washbourn<sup>1</sup>, who obtained negative results with creolin; of Koch and Behring<sup>2</sup>, who obtained negative results with corrosive sublimate; and of Serafini, who also obtained results unfavourable to the intravascular use of antiseptics. Further, the experiments of Fortescue Brickdale<sup>3</sup> are against the utility of the intravascular injection of antiseptics, though in his experiments only small quantities of antiseptics were pitted against the highly resistant *B. anthracis*, e.g. only 1 c.c. of 1% formalin.

The experiments recorded in this paper were undertaken for the purpose of investigating the value of antiseptic injections into the circulation. The antiseptics employed were formalin, guaiacol, and chinisol. The following experiments were first made with the object of ascertaining how much of these substances could safely be injected. The point of chief importance was to determine the maximum non-toxic doses in each case, as it has been shown that tolerance of these drugs cannot be increased by repeated injections.

Healthy full grown rabbits were the animals used in these experiments, and in each case the injections were made into the marginal vein of the ear, with a sterile needle and syringe, and most careful precautions were taken against air embolism. The results are recorded in the following table (Table I).

TABLE I.

	<i>Rabbit D.</i>	<i>Rabbit F.</i>	<i>Rabbit G.</i>	<i>Rabbit H.</i>
	Injected with 8 c.c. Chinisol 1/640 in 0.6% NaCl solution	Injected with 25 c.c. Guaiacol 1/200 in 0.6% NaCl solution	Injected with 10 c.c. Formalin 1/250 in 0.6% NaCl solution	Injected with 15 c.c. Formalin 1/500 in 0.6% NaCl solution
1902				
June 2	2500 grms. (8 c.c.)	2520 grms. (25 c.c.)	2460 grms. (10 c.c.)	1510 grms. (15 c.c.)
„ 3	2550 grms.	2510 grms.	2430 grms.	1500 grms.
„ 4	2480 „	2530 „	2450 „	1520 „
„ 5	16 c.c. of 1/640 chi- nosol intravenously 2540 grms.	2520 „	2480 „	1525 „
„ 6	2520 „	2545 „	2470 „	1520 „
„ 7	2570 „	All well and active, no paralysis.		
„ 8	—			
„ 9	16 c.c. chinisol 2550 grms.			
„ 10	2650 „			
„ 11	2600 „			
„ 12	2660 „	(Total 40 c.c. 1/640 chinisol.)		

<sup>1</sup> *Guy's Hosp. Reports*, 1888.

<sup>2</sup> Behring (1894) *Bekämpfung der Infektionskrankheiten*, p. 35.

<sup>3</sup> *Lancet*, Jan. 10, 1903.

The point next considered was the organism against which the power of these antiseptics should be pitted. The intravenous inoculation of anthrax bacilli was found to produce uncertain results; the duration of the illness and the effect produced depend so much upon the virulence of the particular culture used, and even more so on the amount of emulsion injected. Moreover, *B. anthracis* is a highly resistant organism when tested against antiseptics *in vitro*; and for the purpose of these experiments a more susceptible organism would give a better indication of the value of antiseptic injections.

For this reason experiments were made with the *B. coli communis*, and *B. typhosus*. But the particular cultures used were unsatisfactory. They either caused death in 5 or 6 hours, or produced a lingering illness from which the animals often recovered. Equally unsatisfactory were the results of intravenous inoculation with *Streptococci* and *Pneumococci*. The animals died so quickly that little opportunity was given to investigate their condition.

#### I. *Experiments with Rabbits infected with B. pyocyaneus.*

The *B. pyocyaneus* was found to be the most useful organism, producing uniform and concordant results when inoculated intravenously. Several experiments were undertaken to determine the pathogenic power of this organism. Cultures were made on standardized glycerine-agar, and incubated for 15 hours previous to inoculation. An emulsion was made of the whole of one such agar culture with 5 c.c. of sterile normal saline solution.

Using this emulsion of *B. pyocyaneus* for inoculation a series of eight experiments gave the following results:

1 c.c.	killed rabbits of	1480—2100	grms. in	3—5	days.
2 c.c.	„	„	1530—2210	„	1—3 „
3 c.c.	„	„	1560—2460	„	12—15 hours.
4 c.c.	„	„	1460—2540	„	5—8 „

These results were confirmed from time to time by the control injections made in the course of the following experiments on the efficacy of antiseptics injected intravenously during the course of the disease.

The experiments will be given *in extenso* so that the effect of the antiseptic may be noted in each case.

(1) *Guaiacol solution, 1/200.**Rabbit 1.* 2530 grms.Injected with 2 c.c. emulsion of *B. pyocyaneus* and immediately afterwards with 20 c.c. of guaiacol solution.

Died in 18 hours.

*B. pyocyaneus* recovered at autopsy from the blood of heart in both rabbits.*Rabbit 2.* 2510 grms. (Control).Injected with 2 c.c. of emulsion of *B. pyocyaneus*. No antiseptics injected.

Died in 26 hours.

(2) *Chinosol solution, 1/640 of 0.6% NaCl.**Rabbit 1.* 1780 grms.Injected with 2 c.c. of emulsion of *B. pyocyaneus* and immediately afterwards with 15 c.c. of chinosol solution.

Died in 17 hours.

*B. pyocyaneus* recovered at autopsy from blood of heart of both rabbits.*Rabbit 2.* 1820 grms. (Control).Injected with 2 c.c. of emulsion of *B. pyocyaneus*. No antiseptics injected.

Died in 20 hours.

(3) *Formalin solution, 1/500.**Rabbit 1.* 1860 grms.Injected with 2 c.c. of emulsion of *B. pyocyaneus* and immediately afterwards with 15 c.c. formalin solution.

Died in 20 hours.

*B. pyocyaneus* recovered at autopsy from the heart blood in the case of both rabbits.*Rabbit 2.* 1920 grms. (Control).Injected with 2 c.c. of emulsion of *B. pyocyaneus* but no antiseptics intravenously.

Died in 23 hours.

(4) *Formalin solution, 1/250.**Rabbit 1.* 1940 grms.Injected with 2 c.c. of emulsion of *B. pyocyaneus* and immediately afterwards with 18 c.c. of formalin solution.

Died in 5 hours.

*B. pyocyaneus* was recovered from the blood of the heart of both rabbits at autopsy.*Rabbit 2.* 2100 grms. (Control).Injected with 2 c.c. of emulsion of *B. pyocyaneus*.

Died in 24 hours.

The rabbits in experiments 3 and 4, injected with formalin, began to sneeze before the injection was completed. A watery discharge of nasal mucus soon began, and the rabbit frequently brushed its nose with its paws.

In each of the above experiments the injection was made into the marginal vein of the ear. The ear was previously cleaned and disinfected by scrubbing with iodide of mercury solution of a strength of 1/1000.

As a control to the above intravascular injections of *B. pyocyaneus* followed by antiseptics, experiments were made as to the efficacy of formalin incubated with broth cultures of the bacillus. Broth cultures were mixed with varying quantities of formalin and incubated for 15 hours as follows:

<i>B. pyocyaneus</i> in	1/1000	Formalin broth—no growth.
„ „	1/1500	„ „ —no growth.
„ „	1/2000	„ „ —growth completely arrested.

These experiments show that this bacillus is susceptible to the action of formalin. If, then, the solution of formalin when injected intravenously, acted directly as an intravascular antiseptic, the amounts used in the animal experiments were sufficient to give positive results. But in all cases the injected animals died more quickly than the control animals, and *B. pyocyaneus* was recovered from the blood of the heart in every case.

These experiments show conclusively that the course of a septicaemia, such as that produced by *B. pyocyaneus*, is not checked but rather accelerated by the intravenous injection of the antiseptics used. Moreover, where, as in experiment 4, with 1/250 formalin, a very large dose, 18 c.c. was injected, the growth of the bacilli was not arrested. The formalin was probably rapidly taken up by the tissues. If it had remained in the blood, the amount present would have been amply sufficient, as shown by the control experiments with formalin-broth, to completely arrest the growth of the bacilli. The animal used would have less than 100 c.c. of blood, so that when the blood mixed with the injected formalin the latter would still be present in a strength of about 1/1500, if no formalin escaped from the blood vessels.

From results such as these the value of intravenous injections of antiseptics would seem of but little use in checking the course of the disease produced by the action of *B. pyocyaneus*. And from this it is but fair to infer that the clinical use of intravenous injections of *antiseptics* can have but the very smallest amount of therapeutic value in cases of septicaemia.

## II. *Experiments on Tuberculous Rabbits.*

To investigate the action of formalin in the course of a more chronic disease than the preceding, the following experiments with tuberculous rabbits were undertaken. Rabbits are less susceptible to tuberculosis than guinea-pigs, and hence give a more favourable opportunity for observing the effects of the antiseptics.

In order to produce a definite infection of the lungs, and thus reproduce, in some measure, one of the forms of clinical tuberculosis, the rabbits were infected intravenously, the usual method of peritoneal inoculation not being found suitable.

Some guinea-pigs had previously been infected by subcutaneous inoculations with human tuberculous sputa. From one of these guinea-pigs, after being killed with chloroform, a tuberculous gland was

removed and made into an emulsion with sterile normal saline. Of this emulsion, two equal portions were injected intravenously into two (*control*) rabbits *A* and *B*. Rabbit *A* was soon noticed to be ill and losing weight. It died 9 days after injection, and was found to have been suffering from tuberculous pericarditis, pleurisy, and pneumonia. Rabbit *B* was not obviously affected for some time; but died 27 days after injection, of tuberculous pneumonia.

Two other rabbits, *C* and *D*, were then infected with tuberculosis. Each was injected with 4 c.c. of an emulsion of a guinea-pig's tuberculous gland as before. The immediate effect of the inoculation was *nil*. But in ten days both rabbits had lost weight:

Rabbit <i>C</i>	weighed	2520	grms.,	now	2140	grms.
" <i>D</i>	"    "	2350	"    "	"	2180	"

Formalin injections were now given to the two rabbits to ascertain their effect on the course of the tuberculosis.

*Rabbit C* received 10 c.c. of a 1/500 solution of formalin in normal saline solution intravenously. This caused it to sneeze, and a watery discharge of nasal mucus to run from its nose. The breathing soon became very rapid: 140—150 respirations per minute. In 20 minutes the rabbit was very ill, lying upon its side, and it died in less than 30 minutes from the time of the injection of formalin.

The experiments above recorded, though few in number, appear to indicate that the lethal effect, in this case, was not alone due to the amount of formalin injected (see the experiment on a healthy animal, p. 160). The tuberculosis had made the animal less resistant to the injection of formalin.

The examination of this rabbit's viscera at autopsy showed extensive caseating tubercles throughout the lungs, a fatty and enlarged liver, and a spleen studded with tubercles. Microscopically the lungs were found to be in a condition of acute miliary tuberculosis, due to the *B. tuberculosis*. It was this condition, which, impeding the blood-flow through the lungs, had prevented the rapid passage of the formalin through the pulmonary capillaries. The danger of injecting formalin in this condition is thus very great, as the above experiment shows. Apparently the formalin concentrates its effect on the lungs and hinders their normal functional activity.

*Rabbit D* also received an injection of 10 c.c. of a solution of 1/500 formalin in normal saline solution. The injection produced no

immediate effect, and the rabbit did not appear to be quite as ill as rabbit *C*.

The injections were repeated as follows :

<i>Rabbit D.</i>				Weight of rabbit
10th day after inoculation—	10 c.c. of 1/500 formalin			2180 grms.
14th   "       "	10 c.c.   "   "			1950   "
17th   "       "	10 c.c.   "   "			1750   "
21st   "       "	5 c.c.   "   "			1680   "
24th   "       "	Rabbit died			1630   "

The autopsy on rabbit *D* showed that the lungs and spleen contained numerous tubercles. Microscopically these tubercles contained tubercle bacilli in large numbers.

Rabbits infected, therefore, in this manner with tuberculosis may be expected to die in about a month, or under exceptional circumstances, as in rabbit *A*, in 9 days. The injections of formalin in rabbit *D* would not seem to have affected the course of the disease favourably or otherwise. In the case of rabbit *C* the dangers of formalin injection are demonstrated. The obstruction offered by the miliary tubercles to the flow of the formalin through the lungs, concentrates its effect there, and this, though desirable therapeutically, appears to be disastrous physiologically.

The results of these experiments would seem to show that there are no advantages to be derived from the intravascular use of antiseptics.