After four days of the icebag it was only one-sixth, and two days later there was only a trace of albumen present.

One more case may be related which will show how useful the application of ice may be in a very severe case of nephritis:

H. V., aged 3 years and 10 months, was admitted into the Hospital for Sick Children on November 9th, 1901, having suffered from headache, shivering, repeated vomiting for seven days, swollen face for six days, and bloody urine for two days. On admission he was pale and very restless, with a furred tongue, and temperature of 102.8°. No urine at all was passed that afternoon and evening. He vomited once.

November 10th.—Urine 2 oz., very smoky, contains blood, albumen = ½. No casts. Vomited three times.

November 11th.—Hot-air bath, followed by two leeches over each kidney. Hot-water bottles were placed in the bed, and two icebags were applied over the kidneys. Urine about 4 oz. (not all saved). Vomited five times. In the evening the icebags were removed for four hours. Another hot-air bath was given. The icebags were afterwards replaced and kept in position all the night.

November 12th.—Temperature 101° to 102.2°. Urine about 5 oz. Vomiting troublesome. Rectal feeding adopted.

November 13th.—Child has been very drowsy since admission and restless. Very restless in the evening. Restlessness was increased by the hot-air bath. Temperature rose in the afternoon to 104°, and a patch of dullness was found at the right base, with slight pleural friction. An icebag was placed over the right base as well as over the kidneys. Four hours later the temperature had fallen from 104° to 102°, the pulse from 128 to 100, and the respirations from 50 to 40. The child had been sleeping a good deal. It was observed that he was much less restless while the icebags were in position, and became more restless when they were removed. Urine now contains a few hyaline and corpuscular casts and abundant red cells.

November 14th.—Total urine yesterday 5½ oz., albumen ½. Still vomits anything but barley water; retains nutrients. Temperature 100.3°, pulse 100, respirations 36.

November 15th.—More than 10 oz. of urine yesterday. Friction at right base now not audible, but slight dullness remains. He is now taking malted milk by the mouth and does not vomit.

November 16th.—Better. Takes more interest in his surroundings. More than 13 oz. of urine yesterday.

November 17th.—Last evening the temperature rose to 105.4°, and the amount of urine fell to 8 oz.

November 18th.—Urine yesterday only 5 oz. Temperature 102.8°.

November 19th.—Urine yesterday more than 6 oz.

November 20th.—More urine, 9 oz. and some wet beds. The temperature fell last evening to 97.6°, and the icebags were removed for eight hours; when they were reapplied it was 100.2°; at 6 p.m. it was normal. Urine contains less blood and shows few red blood cells, but many leucocytes with abundant epithelial and granular casts.

November 21st.—Good amount of urine. Icebags left off at night, but replaced during the daytime.

November 25th.—Urine in fair amount; albumen much less. Icebags discontinued altogether, after fourteen days' use.

November 28th.—Urine in fair amount; cannot all be saved. It still contains leucocytes and granular and epithelial casts, but no blood, and only a trace of albumen.

December 5th.—Urine contains one or two granular casts, but no leucocytes, no blood, and only a trace of albumen.

December 10th.—One or two casts. Only a trace of albumen.

In conclusion, I desire to express my thanks to the Council of the Harveian Society for the honour of delivering the Harveian Lectures for 1903.

ON A DYSENTERY ANTITOXIN.

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[PRELIMINARY COMMUNICATION.]

SINCE the discovery of the dysentery bacillus in 1898 by Shiga as the cause of an epidemic of dysentery in Japan, a great deal of attention has been directed to this disease, and the work of Shiga in Japan, Kruse in Germany, Flexner and Strong in America, and others, has established the widespread distribution of the bacillus and its claim to be regarded as the causal agent. Further, the work of Duval and Bassett has shown that in the United States of America this bacillus is in all probability the cause of the summer diarrhoea of infants.

A striking point in the pathology of dysentery is that while the bacilli are found regularly in the mesenteric glands, they are not found in the spleen or other organs, and do not occur in the blood, urine, or milk. In this respect Lentz¹ points out that the disease differs markedly from the septicaemic diseases, such as typhoid, and that it must be regarded as a local infection of the intestinal mucous membrane and corresponding lymphatic glands by the bacillus, the toxin alone

passing into the circulation and giving rise to the typical clinical picture, which, as in the case of cholera, gives the impression of a severe poisoning or toxæmia.

The results of animal experiments bear out this view, as the pathological changes which result from the injection of the living bacillus may be equally produced by the use of dead cultures, showing that these changes are brought about by some toxic body, and not by any vital action of the bacillus.

THE TOXIN OF DYSENTERY.

The following experiments were commenced at the end of last year with a view to investigating the character of this toxic body, and the possibility of obtaining an antitoxin.

The filtrates from ordinary peptone broth cultures of the bacillus are only slightly toxic for animals, but it was found that by employing a more alkaline medium much more toxic filtrates could be obtained. The ordinary alkaline broth, as used for the production of diphtheria toxin (that is, alkaline broth to which normal caustic soda has been added in the proportion of 7 c.cm. per litre), was planted with the bacillus. This was grown at 37° C. for about ten days, filtered through a Pasteur-Chamberland filter, and the filtrate tested on rabbits by intravenous injection. Both Shiga's and Kruse's bacilli were tried, and it was found that the results were approximately the same. The following show some of the results:

Toxins obtained by Growing the Bacillus for Ten Days in Alkaline Broth.

No. of Toxin.	Bacillus.	M. L. D. for Large Rabbits.
No. 1	Kruse	1 c.cm.
" 2	"	"
" 3	"	"
" 4	"	"
" 5	"	"
" 6	Shiga	"

In these tests the minimal lethal dose (M. L. D.) was only approximately determined, that is, the toxin killed at 1 c.cm. and not at 0.5 c.cm.

In the subsequent experiments the bacillus of Kruse (obtained from Kral) was employed exclusively. The effect of growing the bacillus for a longer time was then tried, and it was found that by growing it for a month much more toxic filtrates were obtained—killing a rabbit at from a seventh to a tenth of a cubic centimetre (Tables I and III.)

The susceptibility of various animals to this toxin varies enormously; the rabbit, as shown above, being highly susceptible, but the guinea-pig highly resistant—5 c.cm. of the same filtrate not killing a small guinea-pig, either subcutaneously or intraperitoneally. The horse, as will be seen later, is very highly susceptible. The mouse and monkey are not highly susceptible.

The toxin is fairly stable and is not destroyed by heating at 70° C., for an hour, though 80° C., for an hour destroys it. It is not haemolytic for the corpuscles of the rabbit. The results of the intravenous injection of a lethal dose of the toxin in a rabbit are practically the same as those obtained when the living bacillus is used; after a latent period, varying with the amount of toxin used, severe diarrhoea sets in with paralysis of the limbs, beginning sometimes in the fore and sometimes in the hind limbs, but ultimately affecting both. The animal rapidly loses weight and dies usually in from one to three days. *Post mortem* there is marked congestion of the gut, which contains a slimy mucoid fluid, the lungs shows patches of congestion and often small haemorrhages, the other viscera, as a rule, show no marked naked-eye changes.

At the time these experiments were made the only reference to a soluble dysentery toxin which could be found in the literature was the statement by Lentz² in the article on Dysentery in Kolle and Wasserman's *Handbuch der Pathogenen-microorganismen*, "that the filtrates of dysentery cultures are toxic." More recently, however, in a paper published early this year, Conradi³ states that he was able by a process of "aseptic autolysis," to extract from the dysentery bacillus a soluble toxin, and shortly after this Neisser and Shiga⁴ were able to obtain a similar toxin by suspending the bacilli in saline, killing them by exposure to heat, keeping the suspension for two days at 37° C., and then filtering. Recently Rosenthal⁵ has found that by growing the bacillus in Martin's alkaline broth highly toxic filtrates are obtained. This agrees with the results given above.

IMMUNIZATION OF ANIMALS.

Immunization experiments were tried with the rabbit, goat, and horse. In the case of the rabbit the results were negative, the serum of the immunized animal showing no antitoxic action, although it agglutinated the bacillus at 1 in 100.

A goat was immunized with increasing doses of the toxin, beginning with a tenth of a cubic centimetre, and rising to 200 c.cm. The serum of the animal, taken on the thirteenth day after the last injection, was found to agglutinate the bacillus at 1 in 50.

This serum, as tested against the toxin on rabbits, showed distinct though slight antitoxic power compared with normal goat serum. The animal was bled again on the thirty-third day after the last injection, and the serum from this bleeding was tested. This was found to be much more powerfully antitoxic.

These results in the goat being encouraging it was decided to immunize a horse. The details of the immunization are interesting, as showing the very high susceptibility of the horse to even a weak dysentery toxin. The toxin used in this case was one of which 1 c.cm. was required to kill a rabbit intravenously.

The immunization was begun in December, 1902, by giving 0.5 c.cm. of this toxin subcutaneously, and injections of increasing quantities were made every third day for a period of six weeks, when a dose of 150 c.cm. was reached. After a dose of 2 c.cm. of the toxin the horse had a rise of temperature (102.2°) the same evening, and the next day had very pronounced diarrhoea, and was off his feed. Later on, after a dose of 8 c.cm. diarrhoea again appeared, but with these exceptions the animal appeared to stand the immunization well. On the fifth day, after the last injection of 150 c.cm., however, complete paralysis of the hind legs occurred, and the horse had to be killed.

The immunization of another horse was commenced in April, 1903, and was carried out with great caution, beginning with 0.1 c.cm. subcutaneously, and giving gradually-increasing doses at intervals of not less than a week. The toxin used in this case was one of the same strength—that is, killing a rabbit at 1 c.cm. intravenously. The immunization was well borne, and no symptoms were shown by the animal, and at the end of four months a dose of 250 c.cm. had been reached. The injections were then stopped, and after a rest of a month the horse was bled and the serum tested.

The testing of the antitoxic power of the serum is shown in in Tables II and IV. The tests were carried out by mixing the toxin and serum, keeping the mixture for half an hour to an hour in the incubator at 37° C., and then injecting intravenously in rabbits.

It will be seen from the tables that while normal horse serum shows only a very slight antitoxic action, the immune serum (as shown in Table II) is capable of neutralizing at least 80 minimal lethal doses of toxin. Again, in the test shown in Table IV, 0.02 c.cm. of the immune serum is sufficient to protect a small rabbit against about 4 minimal lethal doses of the toxin.

The prophylactic action of the serum is particularly interesting. This is shown in Tables V and VI. It will be seen that if the serum be given intravenously it protects absolutely against large doses of the toxin given half an hour later. If, however, the serum be given twenty-four hours before the toxin it does not protect, or shows only very slight protection. This may possibly be due to the destruction or excretion of the antitoxin during the intervening twenty-four hours.

As the horse at the time of furnishing the serum had only received a very poor toxin these results must be regarded as showing that the animal is capable of forming a very powerful antitoxin. The immunization is now being continued with a much stronger toxin, and should result in the production of a much more powerful antitoxic serum.

On first testing the serum certain irregularities in the results were observed, a given amount of the serum sometimes protecting the animal completely, and at other times, though saving the animal, failing to completely avert the paralysis and diarrhoea. After several experiments it was found that if the serum and toxin are mixed and immediately injected intravenously into a rabbit paralysis and diarrhoea may occur, but that if the mixture be kept at 37° C., for five minutes or longer, the animals are completely protected, showing that a certain time is necessary for the combination of the toxin and antitoxin. Moreover, if the toxin and antitoxin are cooled to 0° C. this combination takes place more slowly than at 37° C., if at all. (These results are shown in

Table VII and VIII.) This is in accordance with the fact noted by Ehrlich⁶ that the rate of combination of certain toxins and antitoxins varies with the temperature.

The serum of the immunized horse gave complete agglutination with *B. dysenteriae* (Kruse) at 1 in 100 in twenty-four hours. There was no precipitate when the serum was mixed with the toxin, as is observed in the case of animals immunized with typhoid filtrates.

TABLE I.—*Test of Minimal Lethal Dose of Toxin (K8) on Adult Rabbits.* (The toxin was made up to 3 c.cm. in each case, and injected intravenously.)

No. of Rabbit.	Weight.	Dose.	Result.
	grams.		
No. 1 ...	1,545	0.10 c.cm. toxin (K8)	Dead (4 days).
" 2 ...	1,525	0.15 " " "	Dead (4 days).
" 3 ...	1,515	0.20 " " "	Dead (3 days).
" 4 ...	1,480	0.25 " " "	Dead (4 days).

The minimal lethal dose was, therefore, under 0.10 c.cm.

TABLE II.—*Test of Antitoxic Action of Serum of Immunized Horse on Adult Rabbits.* (The serum and toxin were mixed and kept at 37° C. for one hour, and then injected intravenously.)

No. of Rabbit.	Weight.	Dose.	Result.
	grams.		
No. 1 ...	1,300	0.50 c.cm. toxin (K8) + 1 c.cm. immune serum	Lived; no symptoms.
" 2 ...	1,485	1.00 " " " + 1 " " "	Lived; no symptoms.
" 3 ...	1,530	2.00 " " " + 1 " " "	Lived; no symptoms.
" 4 ...	1,980	8.00 " " " + 1 " " "	Lived; no symptoms.
<i>Controls.</i>			
" 5 ...	1,180	0.25 c.cm. toxin (K8) + 1 c.cm. normal serum	Lived; no symptoms.
" 6 ...	1,305	0.50 " " " + 1 " " "	Dead (4 days).
" 7 ...	1,500	0.50 " " " + 1 " " "	Dead (3 days).
" 8 ...	1,700	1.00 " " " + 1 " " "	Dead (3 days).
" 9 ...	1,775	1.00 " " " + 1 " " "	Dead (24 hours).

TABLE III.—*Test of Minimal Lethal Dose of Toxin (K8) for Small Rabbits.* (The toxin was made up to 3 c.cm. in each case and injected intravenously.)

No. of Rabbit.	Weight.	Dose.	Result.
	grams.		
No. 1 ...	600	0.05 c.cm. toxin (K8)	Lived; some diarrhoea.
" 2 ...	620	0.10 " " "	Lived; some diarrhoea.
" 3 ...	695	0.15 " " "	Dead (2 days).
" 4 ...	655	0.20 " " "	Dead (3 days).

The minimal lethal dose was therefore 0.15 c.cm.

TABLE IV.—*Test of Antitoxic Action of Serum of Immunized Horse on Small Rabbits.* The serum and toxin (K8) were mixed, made up to 3 c.cm. with normal saline, kept for half an hour at 37° C., and then injected intravenously.

No. of Rabbit.	Weight.	Dose.	Result.
	grams.		
No. 1 ...	560	0.50 c.cm. toxin (K8) + 0.20 c.cm. immune serum	Lived; no symptoms.
" 2 ...	550	0.50 " " " + 0.10 " " "	Lived; no symptoms.
" 3 ...	535	0.50 " " " + 0.05 " " "	Lived; no symptoms.
" 4 ...	460	0.50 " " " + 0.02 " " "	Lived; no symptoms.
" 5 ...	425	0.50 " " " + 0.01 " " "	Dead (40 hours).
<i>Controls.</i>			
" 6 ...	715	0.50 c.cm. toxin (K8) + 0.20 c.cm. normal serum	Dead (48 hours).
" 7 ...	575	0.25 " " " + 0.20 " " "	Dead (30 hours).

TABLE V.—*Prophylactic Action of Immune Serum.* (Serum given intravenously in right ear; toxin (K8) given intravenously in left ear half an hour later.)

No. of Rabbit.	Weight.	Serum.	Toxin (K8).	Result.
	grams.			
No. 1 ...	1,345	4.0 c.cm.; immune	0.5 c.cm.	Lived; no symptoms.
" 2 ...	1,655	" "	1.0 "	Lived; no symptoms.
" 3 ...	1,705	" "	2.0 "	Lived; no symptoms.
" 4 ...	1,710	" "	2.0 "	Lived; no symptoms.
" 5 ...	1,705	" "	2.0 "	Lived; no symptoms.
" 6 ...	1,715	" "	4.0 "	Lived; no symptoms.
<i>Control.</i>				
" 7 ...	1,670	4.0 c.cm. normal	0.5 "	Dead (20 hours).

TABLE VI.—*Prophylactic Action of Immune Serum.* (Serum given intravenously in right ear; toxin (K8) given intravenously in left ear 24 hours later.)

No. of Rabbit.	Weight.	Serum.	Toxin.	Result.
	grams.			
No. 1 ...	1,635	4.0 c.cm.; immune	2.0 c.cm.	Lived; transient paralysis in forelegs.
" 2 ...	1,370	" "	2.0 "	Dead (4 days) after paralysis and diarrhoea.
" 3 ...	1,555	" "	2.0 "	Lived; transient paralysis in forelegs.
" 4 ...	1,650	" "	4.0 "	Dead (2 days).
<i>Controls.</i>				
" 5 ...	1,970	4.0 c.cm.; normal	0.5 c.cm.	Dead (40 hours).
" 6 ...	1,695	" "	0.5 "	Dead (20 hours).
" 7 ...	1,470	" "	0.5 "	Dead (20 hours).
" 8 ...	1,740	" "	1.0 "	Dead (40 hours).

TABLE VII.—*Table showing that Toxin and Antitoxin do not Combine at Once.* (Injections intravenous in rabbits.)

No. of Rabbit.	Weight in Grams.	Serum.	Toxin (K8).	Serum and Toxin Mixed and Injected.	Result.
1	1,570	1 c.cm. immune	3.0 c.cm.	Immediately	Dead (4 days) after paralysis and diarrhoea.
2	1,425	1 c.cm. immune	3.0 c.cm.	After 1 hour at 37° C.	Lived; no symptoms.

TABLE VIII.—*Table showing Effect of Temperature on the Combination of the Toxin and Antitoxin.* (Injections intravenous in rabbits.)

No. of Rabbit.	Weight in Grams.	Immune Serum.	Toxin (K8).	Serum and Toxin Mixed and Injected After.	Result.
1	1,725	0.5 c.cm.	3.0 c.cm.	5 min. at 37° C.	Lived; no symptoms.
2	1,550	0.5 c.cm.	3.0 c.cm.	4 min. at 0° C.	Dead (32 hours).
3	1,675	0.5 c.cm.	3.0 c.cm.	30 min. at 0° C.	Dead (42 hours).

The antitoxin appears to be stable, and shows no marked change after exposure to a temperature of 65° C. for an hour. Tested both on rabbits and guinea-pigs, the immune serum showed no more protection, either against living or dead cultures of the dysentery bacillus, than did normal serum.

The question naturally arises as to whether the toxin described must be regarded as an intrabacillary toxin which has been extracted from the bodies of the bacilli by the prolonged action of the alkaline broth, or whether it is a true extrabacillary toxin secreted as such by the bacillus. This point is not easily decided, but the fact that the antitoxin does not protect against either the living or dead bacilli would appear to favour the latter view.

From the above results we are forced to the conclusion that by immunization with the toxin it is possible to obtain a purely antitoxic serum which is quite distinct from the antibacterial sera which have been described by Shiga⁷ and Kruse,⁸ and with which excellent clinical results are said to have been obtained.

CONCLUSIONS.

1. By growing the dysentery bacillus in a somewhat highly alkaline broth a soluble toxin is obtained.
2. Certain animals, notably the horse and rabbit, are highly susceptible to this toxin.
3. The toxin is fairly stable, and though destroyed by an exposure to a temperature of 80° C. for an hour, is not destroyed by exposure to a temperature of 70° C. for the same period.
4. When injected into suitable animals, for example, the horse, the toxin gives rise to a powerful antitoxin.
5. The combination of the toxin and antitoxin *in vitro* does not take place immediately, but requires a certain time, and the rate of combination varies with the temperature.

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ON TOTAL EXTIRPATION OF THE STOMACH;
WITH A RECORD OF AN UNSUCCESSFUL
CASE.

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SINCE the publication of Schlatter's case there have been many reported as examples of complete gastrectomy. On reading carefully through the description of the operation it is found that in the majority of these some portion of the stomach—generally at the cardiac end—has been left. Thus, in one report it is said that "the stomach was excised at about 2 in. anteriorly and 3 in. posteriorly from the cardiac end"; and similar statements can be found in many other reports.

HISTORICAL.

The first complete extirpation of the stomach was performed in 1883 by Connor. The patient died on the table. Cases of "extirpation of the stomach" were recorded by Schuchardt (1884), Maydl (1902), and Langenbuch (1894), but in all these a portion of the stomach was not removed. The next "total extirpation"—the first to be successful—was the memorable case of Schlatter's. In this the whole stomach was removed; the microscopical examination of the specimen showed duodenum at the one end and oesophagus at the other. The cut end of the duodenum was closed by suture, and the oesophagus united to the jejunum. The patient, a woman of 56, lived fourteen months, and died of local recurrence. Her health after the operation improved greatly. She was able to take food in good quantity, and she gained in weight. The third operation was performed by Brooks-Brigham in 1898.¹ The patient was a woman aged 66. The duodenum was united to the oesophagus by means of a Murphy button. Recovery ensued, and the patient was alive and well two years after the operation.

The fourth operation was by Maurice Richardson of Boston.² The patient recovered, but died eleven months later of recurrence.

The next case is recorded by Macdonald. The patient was a man aged 38. The duodenum and oesophagus were united by a Murphy button. The patient was alive and well eighteen months after the operation. Kocher removed the whole stomach and a portion of the transverse colon from a woman aged 44. The duodenum and oesophagus were united by suture. The patient died of peritonitis.

Bernays removed the stomach and a portion of the pancreas from a man aged 42. Death occurred in thirty-six hours.

Chavasse operated upon a man aged 64. As it was impossible to unite the oesophagus to the intestine its end was closed by suture and duodenostomy performed. The patient died in a few hours.

Bardeleben removed the entire stomach from a woman