delicacy alone. Almost any good tonic will effect a cure. Many physicians have a preference for phosphate of iron in its popular form, or perchloride of iron as strongly advocated by West, or strychnine as advised by Ringer. Included in this method are all measures which tend to improve the health, such as cold douches, massage, "running wild" in the country, change of air, or any of the many things which we are in the habit of prescribing to improve the general health and tone of our patients. The practice of taking the patient up several times at night is a convenient method of protecting the bed, but it is in no sense a means of cure.

Treatment of the Digestion.

In the second class, evidences of indigestion are to be found more or less prominent, and all the causes which produce intestinal sepsis are to be looked for, and, if possible, removed. These are the cases which are often so easily cured by diet. In the acid form the cutting off of meat alone may be followed by success, and in the alkaline form the use of a non-farinaceous diet is often immediate in its good results. The failure of either diet is due to such method alone not being sufficient by itself to stay the course of an intestinal sepsis once begun. There are, of course, a number of ways of combating intestinal sepsis. A good routine treatment consists in securing a good daily evacuation of the bowels by giving $\frac{1}{4}$ gr. of calomel every night and a mild saline aperient in the morning. In addition one may give one or more of the many drugs which aid intestinal aseptis. Further assistance may be obtained from any of the health-improving methods before mentioned, which can be selected at the discretion of the physician. He must also decide each case on its merits, as to whether medicinal tonics can be used at the same time that the septic condition of the digestive organs is being combated.

ILLUSTRATIVE CASES.

1. Enuresis had existed for a long time in the son, aged 7 years, of a lodging-house keeper. He was at once cured by being taken into hospital and kept on the ordinary hospital diet without any other treatment.

2. A girl, aged 21 years, the servant at another lodging house, was cured as rapidly by the same method.

The obvious cause in each instance was intestinal sepsis from irregular and injudicious feeding.

3. A girl, aged 10, had had enuresis for three months. She had immediate freedom from this symptom while taking a non-farinaceous diet, but for the first six weeks relapse followed the slightest consumption of starchy food.

4. A boy at school with enuresis and highly acid urine showed no improvement when taken off meat. He was, however, rapidly cured by a course of $\frac{1}{4}$ gr. calomel every night, and 5 gr. of salicylate of soda thrice daily.

Breaking the Habit.

In the third class one may look for sources of irritation which might require treatment—for example, worms, fissure in ano, adherent prepuce, etc. This is more especially the case as one may, so to speak, "kill two birds with one stone." That is to say, the operative treatment necessary to cure the local condition, acting strongly on the mind, or by making sleep less profound, frequently breaks the habit of enuresis. And this it may do in spite of the fact that the local condition had nothing whatever to do with the formation of the habit. Other surgical methods, such as blistering the sacrum, blistering the penis, freely cauterizing the urethra, the passing of large metal bougies, and the various ways of using electricity—all act in one or other of these two ways. Equally efficacious and far more rational is it to talk seriously before the patient of the possibility of one or other of these measures having to be adopted if improvement does not immediately occur. This is the class of case which the schoolmaster, much to his satisfaction if the physician has failed, succeeds in curing by corporeal punishment. As, however, he cannot be expected to diagnose as to which of the three classes the case belongs, the odds are against his success, and, as previously pointed out, worse evils than enuresis may result.

Former Treatments.

Of other treatments, one need mention a few which have not been previously dealt with. The success or failure of all others is easily explained if the view herein advocated be adopted.

The limitation of the amount of fluid drunk never gained much reputation—in fact, it rather tends to aggravate than relieve the symptom, by adding to the digestive disturbance.

Belladonna in small doses acts as a tonic to the nervous system, and may, as other tonics, succeed in the first class of cases. When given in semipoisonous doses it acts on the mind, and is then successful by diverting the attention. Professor Fonnagrive thinks it acts by making sleep less profound, so that control of the sphincter muscles is not lost. This is interesting in connexion with Macalister's opinion that belladonna acts better when combined with strychnine. A. Jacobi says belladonna is only useful when there is vesical catarrh.

Sedatives such as chloral and bromide may succeed for a time by blunting the nervous mechanism of micturition, but they do not touch the cause, and their use is consequently unscientific.

CONCLUSION.

In conclusion I would contend that nocturnal enuresis is capable of the simple explanation here given, that order is by this explanation introduced into the chaos of conflicting views and opinions, that reasons are now obvious for the success or failure of the various methods of treatment formerly in use, and that treatment can now be carried out on rational and scientific lines instead of by the empirical and haphazard methods of the past.

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UPON THE PROPERTIES OF AN ANTITYPHOID SERUM OBTAINED FROM THE GOAT.*

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In this communication I propose to give a brief account of the results obtained by the immunization of the goat with the cell juices of the *Bacillus typhosus*. The experiments are a continuation of those already published, which had as their main object the production of an antibody for the endotoxin of the typhoid bacillus.¹ The difficulties to be overcome proved numerous, and served to retard the progress of the work. It will be sufficient for the present to say that the goat was found to be a more suitable animal than the horse for arriving at a solution of the theoretical and practical considerations involved. The experiments on the goat having fulfilled their purpose may now be recorded. That purpose was to determine the best method of producing with the material employed an anti-endotoxin, and of increasing to an adequate degree the antitoxic value of the treated animals' serum. It was the latter point that presented the chief difficulty in the initial stages of the investigation. It is, however, one of fundamental importance in the preparation of any serum which it is proposed to test for therapeutic possibilities. I therefore felt justified in devoting considerable time to the experiments on the goat, in order to arrive at a method that would give the desired result.

During the progress of the experiments two papers have been published by Besredka upon an antibody for the typhoid endotoxin and to these I will in the first instance make reference.² Besredka gives an account of the immunization of a horse with dead and living cultures of the *B. typhosus*. The intravenous injections of the bacilli extended over a period of two years. The horse's serum was then tested against (1) killed and dried cultures of the typhoid bacillus, of which 0.01 gram killed a guinea-pig on intraperitoneal injection; (2) a soluble endotoxin extracted from the dead and dried bacilli, of which $\frac{1}{2}$ c.cm. killed the guinea-pig. The main results were as follows: 10 cg. of the dried horse serum (about 1 c.cm. before drying) neutralized 10 lethal doses of the killed typhoid

*The results of this investigation were communicated on March 8th, 1906, to the Royal Society, with the exception of the subcutaneous experiments, and those upon guinea-pigs, which have since been completed.

culture and 16 doses of the soluble endotoxin. This low titrate was obtained after two years' treatment of the horse with the dead and living cultures of the typhoid organism. These results I shall refer to more particularly at the conclusion of this paper.

EXPERIMENTS.

The typhoid cell-juices used in my experiments were prepared in the following manner: Virulent typhoid bacilli isolated directly from the peritoneal cavity of the guinea-pig were cultivated on nutrient agar in Roux bottles for eighteen hours at blood-heat. The growth was brushed off and washed with distilled water in a centrifuge for half an hour. The living bacilli were then triturated at the temperature of liquid air in the grinding pot already described by Rowland and myself.³ The time allowed was thirty minutes per gram of bacilli. The resultant mass was taken up in 1 in 1,000 solution of caustic potash and spun for two hours. The fluid obtained represented a 10 per cent. extract of the typhoid cell-plasma, along with such bacilli as had not been removed by the two hours' centrifugalization. This was treated with chloroform vapour for half an hour. The cell-juices obtained under these conditions were sterile and toxic on intravenous injection into the test animals employed—goats and rabbits.

The endocellular toxins obtained in the manner described are unstable bodies, and the juices rapidly lost their original toxicity. The experiments with kept juices possessing feeble or no toxicity did not indicate that their injection would lead to any marked tolerance in the animals against fresh and markedly toxic juices. The probabilities were against this easier and less risky method of procedure. Recourse was accordingly made in the later experiments to the use of the fresh and acutely toxic cell-juices. These juices contained on an average 10 to 12 mg. of solid matter.

The fresh juices, an intravenous injection proved, as stated, acutely toxic for the goat. The first goat after an injection of 1 c.cm. died acutely, and $\frac{1}{10}$ c.cm. was acutely fatal to several goats. In two instances $\frac{2}{50}$ c.cm. killed the animals within twelve hours. Death was preceded by acute diarrhoea and collapse. Where death did not ensue the injection of $\frac{2}{50}$ c.cm. was still followed by illness and diarrhoea, and $\frac{1}{30}$ c.cm. rendered certain animals ill but with less acute symptoms. It was obvious that the intravenous injections would have to be very carefully carried out to avoid unduly depressing or killing the animals. A goat after receiving doses of $\frac{2}{50}$ and $\frac{1}{10}$ c.cm. died, whilst another after the injection of $\frac{2}{50}$, $\frac{1}{10}$, $\frac{1}{2}$, and 1 c.cm. died within four hours after the last dose. The subsequent animals consequently received small sublethal doses which were raised very gradually at duly spaced intervals. One injection weekly proved to be the safest procedure, and the same dose was repeated until it failed to produce any toxic action on the animal. A slightly higher dose was then given and repeated in the same manner. This method proved ultimately successful, as only in this way was tolerance established to otherwise fatal doses of the typhoid endotoxin.

In the experiments here recorded, the anti-endotoxic action of the serum was tested by intravenous injections in rabbits. The endotoxin likewise killed rabbits acutely, for example, $\frac{1}{10}$ c.cm., with acute diarrhoea and collapse, at times within two hours, and $\frac{2}{50}$ c.cm. was not infrequently a lethal dose. The conditions were, therefore, sufficiently stringent as regarded any anti-endotoxic action of the treated goat's serum. The toxic cell-juices were titrated for the purpose of each serum test. I satisfied myself that neither the normal serum of the goat or the rabbit possessed any appreciable antitoxic power for the toxins employed. Controls in this respect were found subsequently to be unnecessary. Three c.cm. of normal goat's and rabbit's serum did not neutralize two or ten lethal doses of the endotoxin. The serum of the treated animals was tested against multiple lethal doses of the endotoxin. An estimate was likewise made of the agglutinative and bacteriolytic properties of the serum.

I now proceed to an account of the first successful immunizing experiment:

Billygoat 1.—Received the following intravenous injections of the toxic cell-juices of *B. typhosus*:

May 16th, 1905, $\frac{2}{50}$ c.cm., animal ill; May 24th, $\frac{1}{10}$ c.cm., ill; June 2nd, $\frac{1}{2}$ c.cm., ill; June 9th, $\frac{1}{2}$ c.cm., ill; June 16th, 1 c.cm., ill; June 23rd, 1 c.cm., ill; June 30th, 1 c.cm., ill;

July 7th, 1 c.cm., no symptoms; July 14th, 1.5 c.cm., no symptoms; July 21st, 1.5 c.cm., no symptoms; July 28th, 2 c.cm., ill; August 4th, 2 c.cm., no symptoms; August 11th, 2.5 c.cm., dead.

It was evident that with subsequent animals an even more careful system of dosage would have to be adopted. The goat was bled at intervals and the serum tested. In all instances given in the tables the serum-toxin mixture was kept at blood heat for half an hour previous to intravenous injection into the rabbit.

TABLE I.—*Test of Normal Serum of the Goat.*

Rabbit.	Serum + Endotoxin.	Result.
1	3 c.cm. serum + 1 c.cm. toxin	Dead.
2	2 c.cm. serum + 1 c.cm. toxin	"
3	Control, $\frac{1}{10}$ c.cm.	"
4	Control, $\frac{2}{50}$ c.cm.	Diarrhoea.

Three c.cm. of normal serum did not therefore neutralize 1 c.cm. of a toxin of which $\frac{1}{10}$ c.cm. killed and $\frac{2}{50}$ c.cm. produced acute diarrhoea in the rabbit.

TABLE II.—*Tests of Serum of Treated Goat I.*

Date.	Rabbit.	Serum + Endotoxin.	Remarks.
June 23rd, 1905	1	3 c.cm. serum + 1 c.cm. toxin	Alive.
	2	Control, 1 c.cm. toxin	Dead.
July 7th, 1905	1	3 c.cm. serum + 2 c.cm. toxin	Alive.
	2	3 c.cm. serum + 1 c.cm. toxin	"
	3	2 c.cm. serum + 1 c.cm. toxin	"
	4	Control, 2 c.cm. toxin	Dead in 4 hours.
July 14th, 1905	5	Control, $\frac{2}{50}$ c.cm. toxin	Dead in 18 hours.
	1	3 c.cm. serum + 2 c.cm. toxin	Alive.
	2	2 c.cm. serum + 2 c.cm. toxin	"
	3	1 c.cm. serum + 1 c.cm. toxin	"
July 21st, 1905	4	$\frac{1}{10}$ c.cm. serum + 1 c.cm. toxin	"
	5	Control, $\frac{1}{10}$ c.cm. toxin	Dead.
	6	Control, $\frac{1}{10}$ c.cm. toxin	Acute diarrhoea.
	6	Control, $\frac{1}{10}$ c.cm. toxin	Acute diarrhoea.
Aug. 4th, 1905	1	$\frac{1}{10}$ c.cm. serum + 1 c.cm. toxin	Alive.
	2	$\frac{2}{50}$ c.cm. serum + 1 c.cm. toxin	"
	3	$\frac{1}{100}$ c.cm. serum + 1 c.cm. toxin	Lethal dose not estimated.
Aug. 11th, 1905	1	$\frac{1}{10}$ c.cm. serum + 1 c.cm. toxin	Alive.
	2	$\frac{2}{50}$ c.cm. serum + 1 c.cm. toxin	"
	3	$\frac{1}{100}$ c.cm. serum + 1 c.cm. toxin	Dead.
	4	Control, 1 c.cm. toxin	Dead in 4 hours.
	5	Control, $\frac{2}{50}$ c.cm. toxin	Dead in 18 hours.
	6	Control, $\frac{1}{10}$ c.cm. toxin	Dead in 18 hours.

The death of the goat prevented further tests being made. It will be seen from the table that, following the injections, marked antiendotoxic properties had developed in the serum of the goat. After twelve injections $\frac{1}{10}$ c.cm. of the goat's serum protected a rabbit against 10 ascertained lethal doses of the typhoid antitoxin. This result could not be brought about by 3 c.cm. of the serum of the normal goat. The experiment had therefore been successful; not only had antiendotoxin been produced, but the antitoxic power of the serum had been raised to a marked degree in the course of the three months' immunization of the goat.

It is not my intention in this paper to refer in detail to the production of agglutinins and bacteriolysins that likewise occurred. It will be sufficient to state that whilst the amount of agglutinins present in the serum varied, the highest titrate obtained was with $\frac{1}{1000000}$ c.cm. of the serum. The serum in this dilution produced a distinct clumping of the typhoid bacillus.

The bacteriolytic titrate reached was also high, as at the end of three months $\frac{1}{1000000}$ c.cm. of the serum protected guinea-pigs on intraperitoneal injections against 10 lethal doses of the *Bacillus typhosus*.

The serum of Goat I possessed, therefore, to the above degree agglutinative, bacteriolytic, and antiendotoxic properties.

The next step was to control these results by the immunization of fresh goats, and to carry out the injections in a still more careful manner. The method adopted will be made clear by the following schedule:

Nannygoat II.—Received the following intravenous injections of the toxic cell-juices of *B. typhosus*:

October 13th, 1905, $\frac{1}{20}$ c.cm., animal ill; October 20th, $\frac{1}{20}$ c.cm., no symptoms; October 27th, $\frac{1}{10}$ c.cm., ill; November 3rd, $\frac{1}{10}$ c.cm., no symptoms; November 10th, $\frac{1}{10}$ c.cm., no symptoms; November 17th, $\frac{1}{10}$ c.cm., ill; November 24th, $\frac{1}{10}$ c.cm., ill; December 1st, $\frac{1}{10}$ c.cm., no symptoms; December 8th, $\frac{1}{10}$ c.cm., ill; December 15th, $\frac{1}{10}$ c.cm., no symptoms; December 22nd, $\frac{1}{10}$ c.cm., no symptoms; December 29th, $\frac{1}{10}$ c.cm., ill; January 5th, 1906, $\frac{1}{10}$ c.cm., no symptoms; January 12th, $\frac{1}{10}$ c.cm., no symptoms; January 19th, $\frac{1}{10}$ c.cm., no symptoms; January 26th, $\frac{1}{10}$ c.cm., no symptoms; February 2nd, $\frac{1}{10}$ c.cm., ill; February 9th, $\frac{1}{10}$ c.cm., no symptoms.

Three goats have been successfully immunized by the above method of small and gentle dosage. It will be observed that whilst in the case of Goat I the dose of toxic cell-juice was raised from $\frac{1}{20}$ c.cm. to $2\frac{1}{2}$ c.cm., the final dose reached in the case of the present tests only amounted to $\frac{1}{10}$ c.cm., of juices containing 10 to 12 mg. of solid matter. The results obtained must therefore be ascribed to the quality of the toxins employed in the process of immunization.

TABLE III.—Tests of Serum of Treated Goat II.

Date.	Rabbit.	Serum + Endotoxin.	Remarks.
Dec. 29th, 1905	1	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Alive.
	2	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Dead.
	3	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Alive.
	4	Control, $\frac{1}{10}$ c.cm. toxin	Dead in two hours.
	5	Control, $\frac{1}{10}$ c.cm. toxin	Acute diarrhoea.
Jan. 19th, 1906	1	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Alive.
	2	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Dead.
	3	Control, $\frac{1}{10}$ c.cm. toxin	"
Jan. 26th, 1906	1	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Alive.
	2	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Dead.
	3	Control, $\frac{1}{10}$ c.cm. toxin	"
Feb. 2nd, 1906	1	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Alive.
	2	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	"
	3	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	"
	4	$\frac{1}{20}$ c.cm. serum + $\frac{1}{2}$ c.cm. toxin	"
	5	Control, $\frac{1}{10}$ c.cm. toxin	Dead in 2½ hours.
	6	Control, $\frac{1}{20}$ c.cm. toxin	Dead in 2 hours.
	7	Control, $\frac{1}{10}$ c.cm. toxin	Dead in 18 hours.
Feb. 9th, 1906	1	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Alive.
	2	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Dead.
	3	$\frac{1}{20}$ c.cm. serum + 1 c.cm. toxin	Alive.
	4	$\frac{1}{20}$ c.cm. serum + $\frac{1}{2}$ c.cm. toxin	Dead.
	5	Control, $\frac{1}{10}$ c.cm. toxin	Diarrhoea and collapse.
	6	Control, $\frac{1}{20}$ c.cm. toxin	"

The results detailed in Table III confirm those obtained in the case of the first goat. The figures demonstrate the production of an antiendotoxin in very considerable amount, inasmuch as $\frac{1}{20}$ c.cm. of the serum protected a rabbit against 30 ascertained lethal doses of the typhoid endotoxin. As already stated, normal goat's serum possesses no appreciable antitoxic power. The results were in every respect equivalent to those obtained with Goat I, despite the injection of relatively smaller doses of the toxic cell-juices. The antitoxic power of the serum was raised to the above-stated degree after 16 injections extending over a period of about four months.

In the following experiments the serum was injected separately to the endotoxin into the rabbit:

Rabbit I.—Received 15 lethal doses of the typhoid endotoxin in the right, and 1 c.cm. serum in the left ear vein, followed in twenty minutes by a second injection of 1 c.cm. serum. The animal survived.

Rabbit II.—Received 5 lethal doses endotoxin in the right and 1 c.cm. serum in the left ear vein. The animal survived.

Rabbit III.—Received 5 lethal doses endotoxin in an ear vein, and three-quarters of an hour later, at the onset of toxic symptoms, 2 c.cm. serum were injected. The rabbit survived.

The serum therefore acted when injected simultaneously but separately to the toxin, and also when injected at the onset of toxic symptoms.

The action of the serum when administered subcutaneously was likewise tested. The serum was injected under the skin in doses of 5 c.cm., 3 c.cm., and 1 c.cm. On the following day the three rabbits received intravenously five lethal doses of the typhoid endotoxin, and survived the test. The experiment proved that the serum, when injected subcutaneously, protected animals against multiple lethal doses of the toxin.

Occasion was taken to ascertain the antitoxic action of the serum in respect of the guinea-pig. In the test made it was found that on simultaneous intraperitoneal injection $\frac{1}{50}$ c.cm. of the serum protected guinea-pigs against ten lethal doses of the typhoid endotoxin.

The serum was further tested for any possible action upon an endotoxin derived from an organism other than the typhoid bacillus. I used for the purpose the endotoxin of the cholera bacillus; $\frac{1}{2}$ c.cm. of the serum from Goat II was added to three lethal doses of the cholera endotoxin, and the mixture, after remaining thirty minutes at blood heat, was injected into a rabbit. The rabbit died two and a half hours after the injection. A serum, of which $\frac{1}{50}$ c.cm. neutralized thirty lethal doses of the typhoid endotoxin, did not in the amount of $\frac{1}{2}$ c.cm. neutralize three lethal doses of the cholera endotoxin. The serum was therefore proved to be to this extent specific in its action.

That the inactivation of the typhoid endotoxin is not due to any mere mechanical factor, such as a precipitating action of the serum on the toxic cell-juices, is negated by the following experiment. The goat's serum was added in dilutions of $\frac{1}{10}$, $\frac{1}{100}$, and $\frac{1}{1000}$ c.cm. to the freshly-prepared cell-juices of the typhoid bacillus. At the end of twenty-four hours no precipitin reaction was obtained with the serum, despite its marked anti-endotoxic action.

The agglutinin titrate of the serum of Goat II rose to 1:1,000,000. The bacteriolytic titrate was also high. As in the case of Goat I, $\frac{1}{100000}$ c.cm. of the serum protected guinea-pigs against ten lethal doses of the *B. typhosus*.

GENERAL CONCLUSIONS.

The intravenous injection of the goat with the toxic cell juices of the *B. typhosus* in small and carefully regulated doses, resulted in the production to a very considerable degree of an antiendotoxin—inasmuch as $\frac{1}{20}$ c.cm. of the serum neutralized 30 lethal doses of the typhoid endotoxin. This property did not exist in 3 c.cm. of normal goat's serum.

This titrate was obtained after about four months' immunization of a goat with the toxic cell juices, and is quantitatively much higher than that obtained by so competent an observer as Besredka, even after two years' immunization of a horse with dead and living typhoid bacilli.

The serum acted when injected simultaneously but separately from the toxin; also when injected at the onset of toxic symptoms. Subcutaneous administration was also effective. The serum, in addition to antiendotoxic, possessed agglutinative and bacteriolytic properties.

The serum, whilst neutralizing the typhoid, did not neutralize the cholera endotoxin, and was to this extent specific in its action.

The method which has led to successful results on the goat will next be tested on the horse, in order to ascertain in how far it is feasible to obtain a corresponding rise in the immunizing value of its serum.

Analogous results have been obtained with regard to the production of an antibody for the cholera endotoxin.

I am indebted to Mr. E. T. Thompson for invaluable aid, as well as for an important modification which has rendered the grinding process void of danger.

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POPLAR HOSPITAL.—The report presented to the annual meeting of the Governors of the Poplar Hospital on March 14th showed that its finances are in a satisfactory state. Last year it was able to add £7,000 to its invested funds, which now total £40,000.