

What good would be likely to accrue if the patient suffering from the greatly engorged prostate were submitted to a suprapubic prostatectomy, with the risk of hæmorrhage and an incomplete removal which under these circumstances would thus be incurred? Or, in the other instances I have taken, what would probably result if the patient with the adenomatous-like obstruction were vasectomised or the one with the pendulous fibroid or fibroids were castrated? Practically *nil*. The published experience of the last five years relative to the several operations just referred to is sufficient to suggest answers to these interrogatories.

Putting aside as foreign to this paper the great majority prostatic cases which are amenable to the catheter and the like expedients and do not require operative treatment, for the reason that they get on fairly comfortably without it, my belief is that in vasectomy, McGill's suprapubic prostatectomy, bladder drainage, and possibly castration when the testis is diseased we now have at our disposal reliable means for dealing with exceptional forms of this obstruction, subject to discrimination in their use when the gland is not of a malignant or cancerous nature.

Recognising the difficulty in precisely determining these several limits it should be remembered that vasectomy occupies a different position to the others I have mentioned. When practised under certain conditions, as I have observed in a considerable number of cases operated upon and recorded, it has never been followed by any kind or degree of harm, so far as I am aware.⁵ Together with this it has seldom failed to relieve the patient though not always to the same extent. When this has been the case it was for reasons, I believe, such as have already been indicated and then it left matters either *in statu quo* or open to any other course that seemed advisable. The same cannot be said in respect to other operative expedients of this nature. These measures, however, will be demanded by the urgency of the strain on the urinary system relative to micturition, without reference to any inability that may follow so far as the other factor in the dual function is concerned. Castration, whatever its effects on the prostate may be, extinguishes both desire and capacity, whilst vasectomy only appears to render fecundation impossible by the closure of the seminal ducts. Vasectomy should as far as possible be limited to the larger class of cases which are comprised in the first group, whilst those included in the second and third, by reason of their structural dispositions, have, I believe, furnished the instances in which prostatectomy has been practised with considerable success.

A few words may be added in reference to the individual cases to which these operations have been applied. Vasectomy has been largely successful in diminishing vesical irritability whether associated with catheter life or not. Hardly an instance was observed by me where this was not the case. Thus, it constantly happened that the necessity for using the catheter became less frequent after it and the patient was able to obtain sufficient and continuous rest and sleep. Further, it was found, particularly in old hospital cases, that it enabled people to undertake work which their ailment previously interfered with. Similarly, in many instances it seemed to have averted resort to the catheter, or, more properly speaking, to catheter life—a life which when once commenced is seldom ended. By diminishing the size of the prostate it frequently rendered the use of the catheter tolerable and easy and thus prevented irritation and hæmorrhage which had previously been connected with this process. In other instances it was noticed that though it failed to restore natural micturition it was followed by a partial restoration of this function which gave the individual a greater degree of independence relative to his daily occupations and thus freed him from absolute slavery to the catheter.

Cases where fetid states of the urine, bladder, and kidneys from long-continuing prostatic obstruction and inflammation and where drainage was a necessary part of the treatment often greatly benefited by suprapubic cystotomy. In several of the latter a removal of a portion of the large prostate which had become fibroid was successfully accomplished.

The following case is one that illustrates the points I desire to give some prominence to in this paper. It was that of a man whose vasa I divided early in 1894. He was 64 years of age. He had great irritability of the bladder, was entirely dependent on his catheter, which he used a dozen times or more in the 24 hours, and his urine was offensive and purulent

in spite of careful irrigation. He derived so little benefit from vasectomy that after waiting three months and thinking that he might have an encysted stone somewhere behind his prostate I opened the bladder for exploration above the pubes. All I found was a pendulous fibroid connected with the third lobe of about the size of a small pigeon's egg which I readily twisted off (*vide* Fig. 2). Drainage was continued for 10 days and the wound readily closed. The patient made a good recovery. When I last saw him, about 12 months ago, he was very well and active and could expel the larger quantity of his urine spontaneously. His bladder was tolerant and though he could not empty it completely he had not found it necessary to pass his catheter more than once in the 24 hours since the operation and this he did quite easily. He had for a long time given up washing out the bladder as the urine was quite normal. This was a typical case for suprapubic prostatectomy occurring in a well-preserved man in vigorous health and where a pendulous outgrowth from the prostate was tormenting him just as a stone would do.

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THE ORIGIN OF ANTITOXIN: IS IT PRESENT IN THE BLOOD OF SOME NORMAL ANIMALS?

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I.—The Mode of Action of Antitoxin.

LITTLE by little the mystery which surrounds the origin of antitoxin is being revealed; but the fundamental question whether it is a bacterial product or a secretion of the cells of the living animal is not yet disposed of. The former of these hypotheses is, however, losing ground. On the one hand, it has not been found possible to produce antitoxin directly from toxin by means of the action of various micro-organisms,¹ by heat, or by chemical agents, and the attempts of Smirnow² to do so by electrolysis have not proved convincing; for though electrolysed cultures of the bacillus of diphtheria have been found to possess curative properties their action is feeble compared with that of true antitoxin, and is, moreover, possessed in equal degree by other substances. On the other hand, the suggestion put forward by Ehrlich³ in 1897 that antitoxin is of the same substance as those portions of the protoplasm of certain cells the possession of which is the very cause of their susceptibility to the action of the poison, not only affords a satisfactory explanation of previously known facts, but has received strong support from direct experiments.

When one considers what is the mode of action of poisons in general one is led to believe that they act in a chemical manner upon some constituent of the animal body. Some, may be, have a strong attraction for water only and destroy tissues by robbing them of this fluid; others may possess an affinity for some more special cell-constituent—one which is present in certain organs and groups of cells only. Some observers think that this chemical action results in the formation of a compound which is the real poison. Such may, of course, occur, but if it does it affords no complete explanation of the action of the poison in question, for the action of the new poison has still to be considered. Another possibility presents itself—namely, that the ultimate action of a poison is due to the molecular shock within a living cell which takes place when the poison enters into chemical combination within it with one of its constituents—an action which, as Mr. H. E. Durham has suggested to me, may be illustrated by the breaking of a glass vessel when sulphuric acid and water are mixed within it. If this be the true explanation of the action of any poison, we may conclude that an animal would be susceptible to it only on the condition of its possessing in certain of its cells some substance capable of combining with that poison. The

¹ Metchnikoff: *Annales de l'Institut Pasteur*, Paris, 1897, tome xi., p. 801.

² *Berliner Klinische Wochenschrift*, 1894 and 1895; *Centralblatt für Bakteriologie und Parasitenkunde*, Jena, Band xxi., S. 621.

³ *Die Wertbemessung des Diphtherieheilsersums*, Abdruck aus dem *Klinischen Jahrbuch*, Jena, 1897.

⁵ *Selected Papers on Stone, Prostate, and other Urinary Disorders*. Churchill, 1899.

administration of small quantities of the toxin to a susceptible animal would neutralise more or less of this hypothetical cell-constituents and so disturb the physiological balance—which according to Weigert is maintained in every cell—and lead to the reproduction of the wanting part. This reproduction tends to be carried to excess. So that the result of repeatedly injecting small quantities of the toxin would be to cause an increase of the substance in question. The presence of an excess of this substance in its parent cells would, of course, lead to increased susceptibility on the part of the animal which owned them. (A greatly increased susceptibility to tetanus toxin may, according to Behring,⁴ occur in animals which are being immunised to that substance; and Fraser⁵ makes a similar statement about animals which are treated with snake poison.) But when it had been cast out into the blood-stream it would there be a cause of immunity, for it would be capable of neutralising in a safe place any poison which might be on its way to more delicate susceptible structures. Such, as I understand it, is Ehrlich's view of the origin of antitoxin. Those portions of the cell protoplasm which have the power of entering into chemical combination with a given toxin he has called "Seitenkette." Seitenkette and antitoxin are therefore identical chemical bodies.

The Seitenkette theory has received strong support from the experiments of Wassermann and Takaki⁶ who have shown that tetanus toxin can be rendered harmless by mixing it with the brain or spinal cord substance of animals which are susceptible of tetanus. This observation has been confirmed by Metchnikoff,⁷ who has, moreover, shown that the nervous substance of animals which are insusceptible of tetanus has not this power. This is an important observation, for it not only indicates that the action of the nervous tissues of susceptible animals upon tetanus toxin is not merely of a mechanical nature but that it is in some way connected with their susceptibility and thus offers an explanation of natural immunity.

The facts related above have been confirmed by a number of observers, including Asakawa of Tokio,⁸ who appears to have worked the matter out independently, and by Marie,⁹ Blumenthal,¹⁰ and Milchner.¹¹ Nevertheless, the identity of the neutralising substance present in the nervous tissues of susceptible animals with that present in the blood of immunised animals (i.e., antitoxin) cannot be held to be proved. So far we know only that the former acts when brought into intimate contact with the toxin outside the animal body. Wassermann and Takaki did, indeed, find that it acted when separately injected into the animal, but Marie was unable to confirm this statement, and this point needs further investigation.

One of the chief difficulties in accepting the animal origin of antitoxin has been the great improbability of the living body being able to produce when called upon a considerable number of specific antidotes to an equal number of foreign poisons. The Seitenkette theory disposes of this difficulty, for according to it the poisons in question are not so foreign as they would otherwise appear—had they not the power of combining with a portion of normal cell substance they would not have been poisons at all.

Experimental evidence of the truth of the Seitenkette theory has up to the present time been obtained only in the case of tetanus, and perhaps I should add of botulism toxin,¹² but it is probably applicable to all bacterial toxins as well as to the vegetable toxalbumins, ricin, abrin, croton, &c., for which antitoxins have been found. There is no reason at present to extend it to the action of the vegetable alkaloids or of poisons of simpler composition, for it would appear that no antitoxin to these substances is formed in animals which are repeatedly submitted to the action of these bodies (Gioffredi¹³ claims to have produced a morphia antitoxin in dogs, but this result is in marked contrast to the

failure of those who have worked with other alkaloids and needs confirmation), and it is very doubtful whether they ever confer any true immunity.

II.—The Origin of Antitoxin.

In support of the hypothesis that antitoxin is derived from its toxin it has been urged by Professor Fraser¹⁴ and others that the quantity of antitoxin yielded by an animal during the process of immunisation is proportionate to the amount of toxin introduced. Those who are responsible for the output of diphtheria and tetanus antitoxins would be delighted if this were so, but they know too well that while some horses will yield a powerfully antitoxic serum after the injection of a very moderate amount of toxin, others cannot be got to yield a serum of sufficient antitoxic power for therapeutic use, in spite of the most vigorous treatment. It appears, moreover, that the production of antitoxin continues after the injection of toxin is suspended. Thus Roux and Vaillard¹⁵ have shown that rabbits actively immunised to tetanus might in a short time lose a quantity of blood equal to their total content, and yet the antitoxin power of their serum be practically the same as it was before. Salomonsen and Madsen¹⁶ have seen the antitoxin value of the serum of an animal actually rise during a period when all treatment was discontinued. Their experiment was made as follows. Having immunised a goat with diphtheria toxin until its serum contained five units of antitoxin per cubic centimetre, they discontinued all treatment for two months, during which time the antitoxin value of the serum fell from 5.0 to 0.8 units. At that moment the animal was bled, half of its blood being taken and immediately replaced by the defibrinated blood of another goat. This operation was repeated four hours later, on the following day, and again on the day after. On the last occasion only one-third of the total blood was taken. Thus at the end of this period there remained only one-twelfth of the original blood in the animal. The antitoxin value of the serum was at that moment found to have fallen nearly in proportion to the diminution of the original blood—viz., to 0.13 unit per cubic centimetre, or one-sixth of what it was. Later, however, the quantity gradually increased until in eight days it had reached 0.5 unit per cubic centimetre. It need hardly be said that the blood which was introduced was carefully examined for antitoxin and found to contain none. From this experiment Salomonsen and Madsen concluded that the increase of antitoxin which took place in the blood after the last bleeding could be attributed only to a new production of that substance and that this proves once more that under the influence of the toxin certain cells of the organism have acquired a new and persistent secretory power.

It is possible, no doubt, to interpret these facts somewhat differently—namely, on the assumption of a store of antitoxin in the body from which it is gradually passed into the blood after all injections of toxin have been discontinued. True, Vaillard¹⁷ could not find any such store in the hen injected with tetanus toxin, nor could Dzierzowski¹⁸ in the horse immunised to diphtheria, yet it may be that a store exists, not perhaps of antitoxin but of some antecedent body, some antitoxinogen which is ready to be converted into antitoxin. While this possibility should be borne in mind it cannot be denied that Salomonsen and Madsen's explanation is the more probable.

The question whether antitoxin is formed out of its corresponding toxin, or is an independent product of the animal organisms remains therefore undecided. The balance of evidence, however, seems to favour the latter hypothesis. The matter would be easily settled could a true antitoxin be found in an animal which had never received any of the corresponding toxin, and whose mother had been equally free from its influence. On this point the experiments of Wassermann and others already alluded to cannot be held to be decisive, for, as already pointed out, some doubt still exists as to the identity of the neutralising substance which they found in the nervous tissues of animals susceptible of tetanus and that which is present in antitoxin serum.

⁴ Deutsche Medicinische Wochenschrift, Leipsic, 1893, S. 1254.

⁵ Nature, London, 1896, vol. liii., p. 592.

⁶ Berliner Klinische Wochenschrift, 1898, Nos. 1 and 10.

⁷ Annales de l'Institut Pasteur, Paris, 1898, tome xii., p. 81.

⁸ Centralblatt für Bakteriologie und Parasitenkunde, Jena, 1. Abtheilung, 1898, Band xxiv., S. 166.

⁹ Annales de l'Institut Pasteur, 1898, tome xii., p. 91.

¹⁰ Deutsche Medicinische Wochenschrift, Leipsic, 1898, S. 185.

¹¹ Berliner Klinische Wochenschrift, 1898, No. 17, S. 369.

¹² Kempner and Schepilewsky: Zeitschrift für Hygiene, Leipsic, 1898, Band xxvii., S. 213.

¹³ Brit. Med. Jour., Epit., July, 1898.

¹⁴ Address before the British Medical Association at Edinburgh, THE LANCET, July 30th, 1898, p. 247.

¹⁵ Annales de l'Institut Pasteur, 1893, p. 82.

¹⁶ Ibid., 1898, tome xii., p. 763.

¹⁷ Quoted by Metchnikoff, Annales de l'Institut Pasteur, 1897, p. 801.

¹⁸ Archiv de Scien. Biol., St. Petersburg, tome v., Nos. 2 and 3.

II.—Is Antitoxin present in the Blood of Normal Animals?

Up to the present time no animal which is by nature insensitive or only slightly sensitive to any poison is known to have an antitoxic serum. The hen, so remarkably resistant to tetanus toxin, has no antitoxin in its serum. And the same appears to be true of the scorpion, the tortoise, and the alligator, as well as of fishes, for Metchnikoff¹⁹ found no antitoxin in the blood of these animals after he had administered tetanus toxin to them, and it is to be inferred that there was none at the commencement of the treatment. Rats, mice, and dogs are comparatively insensitive to diphtheria toxin. To kill unit weight of rat requires 1700 times as much toxin as to kill unit weight of guinea-pig.²⁰ Aronson,²¹ indeed, found that the serum of rats prolonged the life of guinea-pigs which were injected with minimal fatal doses of the toxin. But Behring and Wernike,²² Wassermann,²³ Kuprianow,²⁴ and myself²⁵ have found no protective power in the blood of these animals. Calmette²⁶ found that the serum of the mongoose, an animal which is comparatively resistant to snake poison (to kill this little animal with venom 16 times the minimal fatal dose for a rabbit of two kilogrammes is required), only delayed the death of rabbits which had received a minimal dose of venom mixed with the serum. Fraser,²⁷ on the other hand, found that the blood of venomous serpents, which are believed to be resistant to their own poisons, protected against cobra poison, but the doses of venom used was only a little more than the minimal lethal. Lewin²⁸ found that the blood of rabbits which are very tolerant of atropine did not protect other animals against this poison. On the other hand, the serums of a number of *susceptible* animals have been credited with the power of protection against certain poisons. Calmette²⁹ found that the serums of a number of normal animals as well as of some which had been immunised to other poisons protected against snake venom and against certain bacterial and other vegetable toxins to which they had never been exposed. Of these serums, however, doses of several cubic centimetres were required to protect against a single fatal dose of the poison, and often, indeed, they did no more than delay death. M. Pfeiffer³⁰ found that the serum of untreated goats protected against from two to three times the fatal dose of killed cholera culture, or of the filtrate of a cholera culture in which the vibrios had been made to dissolve. On the other hand, it will be remembered that Issaëff³¹ was able to protect guinea-pigs against inoculation with cultures of cholera and other vibrios which would otherwise have certainly proved fatal, by means of previous injections of various substances, such as 0.7 per cent. salt solution, sterile urine, bouillon, 2 per cent. nucleic acid, &c.; and that Phisalix³² showed that injections of cholesterin and tyrosin sufficed to protect animals against doses of snake poison which proved fatal to control animals in from five to six hours. Thus, it would appear that what we may call the general or non-specific protective forces of the body may be put into a state of more than usual efficiency by means of an injection of some irritating or stimulating matter. Among such we may include the serums which we have just considered, and when we consider the feebleness of their protective action when compared with that of the antitoxins we must conclude, as indeed Calmette has already done,³³ that their action is not a true antitoxic action but depends upon cell stimulation, which by causing leucocytosis, or in some way, increases the non-specific powers of resistance of the body. This, however, would not appear to be the complete explanation, because in Calmette's experiments small quantities of the serums were more active when mixed with the

toxins *in vitro* than when they were injected some hours before the poisons. And this, I think, points to some direct action, be it only some delay in the rate of absorption of the poison.

Other animal substances have the power of neutralising toxins. Fraser³⁴ has found that small quantities of rabbit's bile will render harmless the injection of three minimal fatal doses of diphtheria toxin, provided that the two substances are mixed together before injection; and, moreover,³⁵ that snake poison may be made inert by mixing it with the bile of susceptible mammals or of serpents both venomous and innocuous. Whermann³⁶ has shown that both snake poison and tetanus toxin are destroyed by prolonged contact with fresh bile; and Calmette³⁷ finds that bile has no power of neutralising the action of these poisons unless it comes into direct contact with them outside the animal body; he therefore concludes that its action is not antitoxic but digestive.

So far, then, we have not seen the presence of antitoxin demonstrated in the blood of any normal animal. We must now, however, pass on to the consideration of investigations which have pointed to the presence of diphtheria antitoxin in men and horses.

IV.—The Presence of Diphtheria Antitoxin in Normal Human Serum.

A. Wassermann of Berlin³⁸ found that the serum of human beings who, so far as could be ascertained, had never suffered from diphtheria possessed in many cases the power of protecting against diphtheria toxin, even to the extent that one cubic centimetre would protect more or less completely against 10 fatal doses of toxin when mixed with it and injected into a guinea-pig. Of 17 children between one and a half and 11 years of age eight (nearly 50 per cent.) and of 34 adults 28 (nearly 83 per cent.) were found to have such a serum. In some of these instances it may have been higher, for the limit was not ascertained. The serum in all these cases came from hospital patients who were suffering from diseases other than diphtheria. Wassermann held that the greater frequency of diphtheria antitoxin in the serum of adults than in that of children pointed to the relative immunity of man to diphtheria being acquired rather than natural, and was to be attributed to some unrecognised influence of the diphtheria bacillus. Orłowski³⁹ examined the serum of 10 hospital children who had never had diphtheria and found that in about half the serum had a definite power of neutralising the action of diphtheria toxin. Fischl and Wunscheim of Prague⁴⁰ examined the placental blood of 82 infants and found a more or less active antitoxic substance in 68 (83 per cent.). The serum protected against injection both of living culture and of toxin, and not only when culture or toxin were mixed with serum, but also when the former was injected into the subcutaneous tissue and the latter into the peritoneal cavity. Heating to 55° C. for one hour did not destroy the protective body in the serum, which therefore was no alexin but resembled true antitoxin in its resistance to heat and also in that it might be kept for a long time in a cool place without losing its activity.

V.—The Presence of Diphtheria Antitoxin in the Serum of certain Normal Horses.

In 1894 Roux and Martin,⁴¹ struck by the tolerance shown by horses to diphtheria toxin, asked themselves whether the serum of these animals had any antitoxic power. This question they answer as follows: "Le sérum d'un cheval, avant toute expérience, a procuré une survie de quelques jours sur les témoins, aux cobayes qui l'ont reçu, et qui ensuite ont été éprouvés par une culture de bacilles diphthériques." No mention is made of the quantities of serum or toxin used. They go on to say that "ce cheval a supporté d'emblée l'injection sous-cutanée de 5 c.c. de toxine diphthérique, sans malaise aucun. Un œdème qui a duré 12 heures s'est formé au point d'injection, et la température s'est élevée le soir de 0.5°." By which they imply that this animal was more resistant to the toxin than usual.

¹⁹ Annales de l'Institut Pasteur, 1897, tome xi., p. 801.

²⁰ Cobbett: Brit. Med. Jour., vol. i., 1899.

²¹ Berliner Klinische Wochenschrift, 1893, Nos. 25 and 26.

²² Zeitschrift für Hygiene, Leipzig, 1892, Band xii., S. 12.

²³ Deutsche Medicinische Wochenschrift, 1894, Band xx., V.B., S. 20.

²⁴ Centralblatt für Bakteriologie und Parasitenkunde, Jena, Band xvi., S. 415.

²⁵ Loc. cit.

²⁶ Annales de l'Institut Pasteur, 1895, tome ix., p. 225.

²⁷ Loc. cit., p. 596.

²⁸ Deutsche Medicinische Wochenschrift, Leipzig, 1899.

²⁹ Loc. cit.

³⁰ Zeitschrift für Hygiene, Leipzig, 1895, Band xx.

³¹ Ibid., 1894, Band xvi., p. 287.

³² Comptes Rendus de la Société de Biologie, Paris, 1898, tome v., No. 5.

³³ Annales de l'Institut Pasteur, 1898, tome xii., p. 343.

³⁴ Brit. Med. Jour., vol. ii., 1897, p. 595.

³⁵ Ibid., p. 125.

³⁶ Quoted by Calmette, Annales de l'Institut Pasteur, 1898, tome xii., p. 344.

³⁷ Loc. cit.

³⁸ Deutsche Medicinische Wochenschrift, Leipzig, 1894, V.B., S. 120.

³⁹ Deutsche Medicinische Wochenschrift, Leipzig, 1895, p. 400.

⁴⁰ Prager Medicinische Wochenschrift, 1895. Ref. Centralblatt für Bakteriologie und Parasitenkunde, Band xix., p. 652.

⁴¹ Annales de l'Institut Pasteur, 1894, tome viii., p. 615.

In 1894 I made some experiments with the serum of two normal horses.⁴² The serum of one, a young chestnut Suffolk cart-horse, failed to show any protective action when one, two, three, five, six, and 10 cubic centimetres mixed with from one to 1.5 fatal doses of toxin were injected into guinea-pigs; but 10 and five cubic centimetres when mixed with the smallest certainly fatal dose of toxin seemed to prolong life a little. The serum of the second horse, a bay cob of some nine years or more, on the other hand, protected in doses of 2.5 cubic centimetres against 10 times the quantity of toxin fatal in 48 hours when mixed with the latter before injection, while 0.5 cubic centimetre failed to do so. Moreover, 1.45 cubic centimetres protected against five times the minimal dose of broth culture fatal in 48 hours, while 0.56 cubic centimetre failed. The horse which yielded the first serum proved very sensitive to the toxin. 0.7 cubic centimetre of a weak toxin (minimal fatal dose for 500-gramme guinea-pigs = 0.1 cubic centimetre), with an equal volume of Gram's solution of iodine, caused a somewhat severe constitutional disturbance, accompanied by shivering, profuse sweating, very rapid respiration, and a rise of temperature to 104° F. A similar dose given to the other animal produced a scarcely appreciable disturbance. The susceptibility of these animals, therefore, varied inversely with the protective action of their serums. Meade Bolton⁴³ of Philadelphia tested the serum of 12 horses with the result that "three were found to possess antitoxin of such a strength that three cubic centimetres was capable of neutralising 10 times the minimal fatal dose of toxin for guinea-pigs." The other nine yielded serums which exerted no influence even in doses of five cubic centimetres; thus he says "there was either a notable amount of antitoxin present or none at all." Though the author freely speaks of "antitoxin" being present he makes no attempt to show that the protective substance was really antitoxin. Recently I have made some experiments with the object of solving this problem.

The Writer's Recent Experiments.

The serums of 14 horses were examined. Some of these proved toxic to certain guinea-pigs, killing occasionally an animal in a few minutes or in an hour or two. This, however, did not, as a rule, interfere with the investigation of the protective property of the serums, because it appeared that only a very small number of guinea-pigs were susceptible to the poisons in the doses employed. Three of the serums, however, proved so frequently fatal that it was impossible to find out whether or no they contained any substance capable of protecting against diphtheria toxin.⁴⁴ Of the remaining 11, two were obtained from the horse-slaughterer (Nos. 2 and 9, Table I.) and may possibly have come from diseased animals; two (Nos. 10 and 11) came from animals already injected many times with cultures of streptococci and typhoid bacilli respectively; the others were obtained from new horses which were afterwards used for the production of diphtheria antitoxin. They were therefore under constant observation and there can scarcely be any doubt that they were perfectly healthy animals. The serums of these horses, drawn with all necessary precautions, were preserved without any antiseptic with the exception of Nos. 10 and 11 to which some tricresol had been added. Their power of protecting against diphtheria antitoxin was tested in one or more of the following ways: 1. Toxin and serum were mixed and made up to four cubic centimetres with normal salt solution and injected into the subcutaneous tissue of guinea-pigs of about 250 grammes weight. The quantity of serum was constant—viz., one cubic centimetre—and the quantity of toxin varied between one and 75 minimal fatal doses. 2. Serum and toxin were injected separately, (a) the former into the subcutaneous tissue of the abdominal wall on one side of the body and the latter into the corresponding part on the opposite side on the next day; and (b) the serum into the peritoneal cavity and the toxin into the subcutaneous tissue immediately after. It was not thought necessary in all cases to determine the degree of protective power within narrow limits. Consequently it has been thought advisable to set down in the table the largest quantity of toxin which was rendered harmless and the smallest which proved fatal. These quantities of toxin are expressed in minimal fatal doses—that is, quantities which proved fatal to 250-gramme guinea-pigs within four days.

TABLE I.—*Antitoxic Action of Normal Horse Serum.*

Serum of presumably normal horses.	Serum and toxin mixed and injected subcutaneously.			Serum subcutaneously; toxin subcutaneously next day.			Serum intra-peritoneally; toxin subcutaneously immediately after.		
	Quantity of serum in cubic centimetres.	Quantity of toxin in M.F.D.'s.		Quantity of serum in cubic centimetres.	Quantity of toxin in M.F.D.'s.		Quantity of serum in cubic centimetres.	Quantity of toxin in M.F.D.'s.	
		Maximum non-fatal.	Minimum fatal.		Maximum non-fatal.	Minimum fatal.		Maximum non-fatal.	Minimum fatal.
No. 1	1.0	38.0	75.0	2.0	25.0	—	1.0	15.0	—
" 2	1.0	28.0	31.0	—	—	—	1.0	2.0	—
" 3	1.0	10.0	20.0	1.0	2.0	—	—	—	—
" 4	1.0	10.0	12.5	2.0	3.0	—	1.0	3.5	5.5
" 5	1.0	5.0	10.0	—	—	—	—	—	—
" 6	1.0	3.5	5.0	2.0	2.0	3.0	—	—	—
" 7	1.0	—	1.5 (a)	2.0	—	1.25	1.0	—	1.25
" 8	1.0	1.0	1.5 (b)	1.0	—	2.0	—	—	—
" 9	1.0	1.0 (c)	1.5 (d)	—	—	—	—	—	—
<i>Serum of horses immunised to diseases other than diphtheria.</i>									
No. 10. Anti-streptococcus	1.0	62.0	67.0	2.0	3.0	—	1.0	25.0	33.0
No. 11. Anti-typhoid ...	1.0	10.0	11.0	—	—	—	—	—	—

† Signifies the death of the animal.

(a) † In three days; control died in four days after receiving one minimal fatal dose of toxin. (b) † In five days; control died in four days after receiving one minimal fatal dose of toxin. (c) † In eight days; control died in four days after receiving one minimal fatal dose of toxin. (d) Died paralysed on twenty-seventh day.

Of the 11 serums eight were found to have a well-marked power rendering harmless the injection of diphtheria toxin. Of the latter six, in doses of one cubic centimetre, sufficed to protect against at least 10 fatal doses, when toxin and serum were mixed together; the other two had somewhat less action. The remaining three serums had little or no action, and failed in doses of one cubic centimetre to protect against one and a half fatal doses of toxin. Several of the more active serums were found to protect against considerable quantities of toxin, even when they were not allowed to come in contact with the latter outside the animal body. The degree of protective action was in some instances very considerable. Thus one cubic centimetre of No. 1 and No. 2 protected against more than 38 and 28 fatal doses respectively, and an antistreptococcus serum protected against 62. Professor Sims Woodhead tells me that this degree of protective power has been surpassed in two serums from apparently normal horses which he tested, and which contained in each cubic centimetre the protective power of a whole unit of antitoxin. So far these results merely confirm previous experience and show that the serum of many apparently normal horses possesses the power of neutralising the action of diphtheria toxin, both when mixed with it *in vitro* and when the two are injected separately into the animal's body. In this respect and in that a small quantity is capable of neutralising many fatal doses of the poison it resembles the serum of an immunised animal.

VI.—Is the Power of Neutralising the Action of Diphtheria Toxin which the Serum of some Normal Horses possesses due to the Presence of Antitoxin?

The extraordinary activity of some of these serums in neutralising the toxin is unapproached by that of any known substance other than antitoxin, and this makes it extremely probable that they owe their protective power to the presence of the same body which is the cause of the activity of the serum of an immunised animal. The following experiments were undertaken in the hope of establishing the truth of this surmise.

Before describing the actual experiments I must explain the principle upon which they were based. The distinctive feature of an antitoxin, as Ehrlich⁴⁵ has shown, is that a

⁴² Journal of Pathology and Bacteriology, London and Edinburgh, vol. iii., p. 328.

⁴³ Journal of Experimental Medicine, New York, 1896, vol. i., p. 543.

⁴⁴ Journal of Physiology, London and Cambridge, vol. xxiv., p. 29.

⁴⁵ Loc. cit.

given quantity will neutralise a very different number of minimal fatal doses of different filtrates; a fact which he explains on the hypothesis that they contain not only toxin but also a variable proportion of harmless toxoids which also combine with the antitoxin. Now if the serum of certain normal horses owes its activity to antitoxin, a given quantity of it also will neutralise a variable number of minimal fatal doses of different filtrates; and, moreover, *the numbers of fatal doses of two given filtrates neutralised by a fixed quantity of normal horse serum will have the same ratio to one another as the numbers of fatal doses of the two filtrates neutralised by a unit of standard antitoxin.* On the other hand, I think it will be granted that a body which owes its protective action to no chemical affinity for the poison in question, but which acts rather as a cell stimulant, or in some other way causes the body to put its non-specific defences into better order, may be expected to neutralise the action of about the same number of minimal fatal doses of different filtrates, no matter what proportion of harmless toxoids they may contain, for with these latter it has no concern. This, then, was the plan—to determine whether a given quantity of the active normal horse serum would neutralise of two dissimilar filtrates the same number of fatal doses, or whether it would neutralise the same relative number of fatal doses as were neutralised by a unit of antitoxin. And since the test dose (*prüfungs-dosis*) of a filtrate is that quantity which just suffices to kill a guinea-pig of 250 grammes within four days when injected mixed with a unit of antitoxin, it was sufficient for my purpose to determine whether a given quantity of the normal serum in question neutralised of the two filtrates an equal number of fatal doses, or the same multiple or fraction of the two test doses. Now I happened to possess two filtrates which were very dissimilar, the test dose of one containing 119 fatal doses, while the test dose of the other contained only 58. The evidence of the truth of this statement is as follows: Filtrate No. 1 was sown August 1st, 1898, and filtered after 11 days' growth. Six weeks later its minimal dose, certainly fatal within four days to a guinea-pig of about 250 grammes, was 0·01 cubic centimetre. Six months after that it had not appreciably altered (see Table II.). The test dose (=that quantity which when mixed with one unit of standard antitoxin and injected into guinea-pigs of about 250 grammes weight is invariably fatal within four days) of this filtrate was, in April, 1899, rather greater than 0·67 cubic centimetre. It

TABLE II.— <i>Estimation of Minimal Fatal Dose of Toxin No. I.</i>		
Date and weight of animal.	Toxin.	Result.
1898.	c.c.	
April 28th; 280 grammes.	0·0075	† Ninth day.
Oct. 7th; 250 grammes.	0·008	† Third day.
Oct. 4th; 250 grammes.	0·0085	† Second day.
Oct. 4th; 250 grammes.	0·009	† Fourth day.
Oct. 4th; 250 grammes.	0·0095	† Seventh day.
Sept. 28th; 280 grammes.	0·01	† Fourth day.
Oct. 19th; 280 grammes.	0·01	† Fourth day.
1899.		
April 5th; 250 grammes.	0·009	† Third day.
March 27th; 250 grammes.	0·01	† Sixth day.
April 5th; 250 grammes.	0·011	† Fourth day.

TABLE III.— <i>Estimation of the Test Dose of Toxin No. I., Sown August 1st, 1898; Filtered August 12th, 1898.</i>			
Date and weight of animal.	Toxin.	Anti-toxin.	Result.
1899.	c.c.		
March 30th; 230 grammes.	0·62	1 unit	Small swelling; paralysis; † thirtieth day.
April 5th; 265 grammes.	0·63	"	Large swelling; paralysis; lived.
March 30th; 250 grammes.	0·64	"	† Fifth day.
April 7th; 240 grammes.	0·65	"	† Twenty-fifth day.
March 30th; 260 grammes.	0·66	"	† Third day.
April 5th; 265 grammes.	0·67	"	† Sixth day.

TABLE IV.— <i>Minimal Fatal Dose of Toxin No. II., Sown Nov. 19th, 1898.</i>		
Date and weight of animal.	Toxin.	Result.
1898.	c.c.	
Nov. 25th; 250 grammes.	0·0035	Large swelling; necrosis; lived.
Nov. 25th; 255 grammes.	0·004	† Seventh day.
Nov. 28th; 250 grammes.	0·0042	† Eighth day.
Nov. 28th; 245 grammes.	0·004	† Third day.
Nov. 28th; 240 grammes.	0·0046	† Fourth day.
Dec. 24th; 230 grammes.	0·004	Small swelling; lived.
Dec. 24th; 230 grammes.	0·0042	Small swelling; lived.
Dec. 16th; 250 grammes.	0·0044	† Second day.
Dec. 19th; 240 grammes.	0·0044	† Third day.
1899.		
March 8th; 250 grammes.	0·0043	Necrosis; lived.
March 8th; 260 grammes.	0·0044	Necrosis; lived.
March 21st; 270 grammes.	0·0044	† Second day.
March 17th; 270 grammes.	0·00445	† Second day.
March 13th; 255 grammes.	0·0045	† Fourth day.
March 17th; 270 grammes.	0·00455	† Second day.

TABLE V.— <i>Estimation of the Test Dose of Toxin No. II.</i>			
Date and weight of animal.	Toxin.	Anti-toxin.	Result.
1898	c.c.		
Nov. 25th; 240 grammes.	0·45	1 unit.	Small swelling; lived.
Nov. 25th; 255 grammes.	0·5	"	† Ninth day.
Nov. 29th; 240 grammes.	0·525	"	† Third day.
Nov. 29th; 240 grammes.	0·55	"	† Third day.
Nov. 29th; 230 grammes.	0·575	"	† Second day.
Nov. 22nd; 235 grammes.	0·6	"	† Second day.

TABLE VI.— <i>Normal Horse Serum No. 4. Filtrate No. I.</i>					
Date and weight of animal.	Quantity of filtrate in			Quantity of serum in cubic centimetres.	Result.
	cubic centimetres.	fatal doses.	test doses.		
1898.					
Dec. 6th; 260 grammes.	0·075	7·5	0·011	1·0	Great local infiltration; recovered.
Dec. 6th; 260 grammes.	0·08	8·0	0·0118	1·0	Great local infiltration; recovered.
Dec. 12th; 225 grammes.	0·08	8·0	0·0118	1·0	Great local infiltration; recovered.
Dec. 2nd; 225 grammes.	0·1	10·0	0·0147	1·0	† Third day.
Dec. 2nd; 220 grammes.	0·12	12·0	0·0177	1·0	† Third day.
<i>Filtrate No. II.</i>					
Dec. 6th; 240 grammes.	0·0656	15·0	0·0125	1·0	Great local infiltration; recovered.
Dec. 16th; 290 grammes.	0·07	16·6	0·013	1·0	† Eighth day.
Dec. 2nd; 225 grammes.	0·07	16·6	0·013	1·0	† Fourth day.
Dec. 2nd; 225 grammes.	0·0875	20·8	0·015	1·0	† Third day.
Dec. 2nd; 240 grammes.	0·105	25·0	0·02	1·0	† Second day.

was taken to be 0·68 cubic centimetre (see Table III.). The test dose of this filtrate being 0·68 cubic centimetre and the minimal fatal dose 0·01 centimetre, the former contained $\frac{0·68}{0·01} = 68$ minimal fatal doses. Filtrate No. 2 was sown Sept. 19th, 1898, and was filtered

three days later. Its minimal fatal dose in December was 0·0044 cubic centimetre. In the following March it was still unchanged. The test dose of this filtrate was in November 0·525 cubic centimetre (see Table IV.). Since the minimal fatal dose remained constant during the next five months it may be assumed that the test dose also remained unchanged (see Table V.). The test dose of this filtrate therefore being 0·525 cubic centimetre and the minimal lethal dose 0·0044

TABLE VII.—*Normal Horse Serum No. 2.*
Toxin No. I.

Date and weight of animal.	Quantity of toxin in			Quantity of serum in cubic centimetres.	Result.
	cubic centimetres.	fatal doses.	test doses.		
1899. April 10th; 250 grammes.	0·145	14·5	0·214	1·0	Slight local infiltration. Remained well two weeks; died paralysed on the twenty-third day.
April 10th; 250 grammes.	0·163	16·3	0·24	1·0	† Seventh day.
April 10th; 250 grammes.	0·177	17·7	0·26	1·0	† Fourth day.
April 10th; 235 grammes.	0·195	19·5	0·286	1·0	† Third day.
<i>Toxin No. II.</i>					
March 30th; 230 grammes.	0·1125	25·6	0·214	1·0	Slight local infiltration; alive and well on thirty-second day; weight 290 grammes.
April 4th; 270 grammes.	0·126	28·6	0·24	1·0	Medium local infiltration; died paralysed on nineteenth day.
March 27th; 230 grammes.	0·14	31·8	0·26	1·0	† Fifth day.
March 27th; 230 grammes.	0·15	34·0	0·286	1·0	† Third day.

TABLE VIII.—*Anti-Typhoid Horse Serum.*
Toxin No. I.

Date and weight of animal.	Quantity of toxin in			Quantity of serum in cubic centimetres.	Result.
	cubic centimetres.	fatal doses.	test doses.		
1899. April 10th; 235 grammes.	0·058	5·8	0·0857	1·0	Local infiltration; necrosis; died paralysed on twenty-ninth day.
April 10th; 235 grammes.	0·064	6·4	0·0943	1·0	† Seventh day.
April 10th; 235 grammes.	0·07	7·0	0·103	1·0	† Fifth day.
April 10th; 240 grammes.	0·0815	8·16	0·12	1·0	† Fourth day.
<i>Toxin No. II.</i>					
March 20th; (1) 270 grammes; (2) 280 grammes.	0·045	10·0	0·0857	1·0	* L. S., necrosis; alive and well on seventeenth day; 285. * L. S., necrosis; alive and well on seventeenth day; 270.
April 4th; 260 grammes.	0·0495	11·0	0·0943	1·0	† Seventh day.
March 29th; 230 grammes.	0·054	12·0	0·103	1·0	† Fifth day.
March 27th; 235 grammes.	0·0675	15·0	0·12	1·0	† Second day.

* L. S. = large swelling at the seat of injection. The numbers refer to the weight in grammes of the animal on the date of the last note.

cubic centimetre, it follows that the test dose contained $0·525 = 119$ fatal doses. Here, then, were two filtrates 0·0044 which contained such different proportions of toxoids to toxin that with them I might hope to decide whether the normal horse serums were affected by the toxoids in the same way as the true antitoxic serum is. Three of the serums (Nos. 2, 4, and 11) were tested against these two filtrates with the results given in Tables VI., VII., and VIII.

It will be seen that of each of these serums one cubic centimetre protected against exactly the same fraction of the test dose of each filtrate (i.e., against the same relative number of minimal fatal doses as the unit of true antitoxin had done) and, in other words, against multiples of the minimal fatal doses of each filtrate which differed much, but which bore the same ratio to one another as did the numbers of fatal doses of each filtrate neutralised by a unit of antitoxin. Thus the protective action of the normal horse serums was found to depend upon the presence of a body which combined both with the toxin and with the toxoids of diphtheria just as true antitoxin does. I believe that these experiments afford a proof of the identity of these substances.

But if it be granted that the serum of certain horses which have never been subjected to any process of immunisation contains true diphtheria antitoxin it by no means follows that this is a normal constituent of these animals; indeed, the fact that it is absent in a considerable number is opposed to this conception. On the other hand, I understand that horses are not known to suffer from any affection caused by the diphtheria bacillus. Nevertheless, this micro-organism may affect them in some way not yet discovered, or may perhaps partially immunise them while growing as harmless parasites in some portion of the alimentary canal. The presence of antitoxin in these animals cannot therefore be held to throw any light on the origin of that substance.

It is well known that the value of different horses for the purpose of yielding diphtheria antitoxin varies enormously. If any method of selecting the right animals at the commencement of immunisation were known much time and work would be saved. One therefore asks whether the suitability of a horse for this purpose has any relation to the presence or absence of antitoxin in the blood before any treatment is begun. To this question Meade Bolton⁴⁶ gave a negative answer. My own experience is not yet sufficiently advanced to warrant any expression of opinion. But the matter is being now worked out by Dr. Dowson and myself and we hope shortly to make some communication about it.

I should like to express my thanks to Dr. Dowson for having very kindly provided me with many of the serums tested in the experiments which have just been described. It was our intention at the outset to do the work conjointly, but the great pressure of other business has unfortunately prevented him from taking part.

THE AFTER-TREATMENT AND POST-OPERATIVE COMPLICATIONS OF CELIOTOMY FOR PELVIC DISEASE IN WOMEN.

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THOUGH the larger number of cases of abdominal section for pelvic disease in women stand to succeed or to fail on the peculiarities of each case, and the individual skill and asepsis of the operator, a certain proportion are, and always will be, dependent for their result upon the post-operative treatment and the care and watchfulness with which it is carried out. In this paper I shall endeavour to set forth my experience and practice founded on a yearly record of between 200 and 300 cases.

THE ROUTINE TREATMENT.

The operation takes place in the afternoon and on returning to the ward after it the patient is made comfortable with