The Lister Institute of Preventive Medicine (late Jenner Institute of Preventive Medicine) / with notes on serum therapeutics by members of the staff of the Institute.

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THE

Lister Institute

OF

Preventive Medicine

LATE JENNER INSTITUTE OF PREVENTIVE MEDICINE)

With Notes on Serum Therapeutics

BY MEMBERS OF THE

STAFF OF THE INSTITUTE

[illegible]

(Published by the Authority of the Governing Body)

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THE

LISTER INSTITUTE

OF

PREVENTIVE MEDICINE

(Late Jenner Institute of Preventive Medicine)

ROYAL COLLEGE OF SURGEONS ENGLAND

WITH NOTES ON

SERUM THERAPEUTICS

BY

MEMBERS OF THE STAFF OF THE INSTITUTE

(Published by the Authority of the Governing Body)

London

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1904

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THE

LISTER INSTITUTE

OF

PREVENTIVE MEDICINE.

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THE LISTER INSTITUTE OF PREVENTIVE MEDICINE

(Late the Jenner Institute of Preventive Medicine).

The Institute, now known as the Lister Institute, owes its inception to the Committee appointed at a meeting held at the Mansion House, London on July 1, 1889, for the purpose of taking steps to present M. Pasteur with a grateful acknowledgment from this country of his gratuitous kindness in Paris to over 200 British patients who had been bitten by rabid animals.

The acknowledgment took the form of a donation of £2,000 to M. Pasteur for the use of the Institut Pasteur in Paris. At the same time the Committee realised the want in the United Kingdom of an institute similar in character and purpose to the Institut Pasteur in Paris, or to the Hygienic Institute in Berlin, and others established on the Continent for scientific research into the causation and prevention of the various infective diseases of men and animals.

With the idea of meeting this need the British Institute of Preventive Medicine was incorporated on July 25, 1891, and the objects of the Institute were set forth in a Memorandum of Association, viz.: "To provide Laboratories, to appoint a Scientific Staff, to institute Lectures and

Demonstrations, to issue Publications of the Transactions of the Institute, and to found a Library."

A Council, presided over by Sir Joseph, now Lord, Lister, and representing in its members biological, chemical, medical, veterinary and agricultural science, was appointed to govern the affairs of the newly-founded Institute.

A public appeal was made for the necessary funds, and the response was favourable. It included a donation of £20,000 from the trustees of the late Mr. Richard Berridge, and another of £10,000 from the Grocers' Company, who had already anticipated the same idea in the foundation from their funds of special Research Scholarships. Certain noblemen and other friends of science, especially amongst the medical profession, warmly supported the appeal.

The College of State Medicine was amalgamated with the Institute in 1893, and in this way temporary premises were obtained at Great Russell Street, a scientific staff was appointed, and provision was made for research work, etc. In the meanwhile the late Duke of Westminster granted, on terms which practically meant a large personal contribution from himself, a magnificent site facing the Thames at Chelsea Gardens.

The Council then proceeded to build, from the designs of Mr. Waterhouse, R.A., the permanent headquarters at Chelsea shown in the photograph opposite. These were opened in May, 1897.

The development of serum therapeutics led to the establishment of an antitoxin department at Sudbury, near Harrow, where anti-diphtheria serum was prepared for the first time in this country.

In 1898 the Institute received a donation from the Jenner Memorial Committee of a considerable sum which

Lister Institute, Chelsea Gardens, London, S.W.

A Laboratory at Chelsea.

had been subscribed to perpetuate the memory of Edward Jenner and his work. The name of the Institute was thereupon changed to that of the Jenner Institute of Preventive Medicine.

But after this name had been agreed upon it was found that a commercial firm in London engaged in the preparation of vaccine lymph was already trading under the name of "The Jenner Institute for Calf Lymph," and therefore had a prior legal claim to the title of "Jenner Institute," which the proprietor was unwilling to relinquish. The two Institutes had no connection, and at first it was hoped that no confusion would arise between them. This hope was not, however, realised. After a year or two, the two Institutes were commonly thought to be one and the same, until at length the inconvenience became so great that it was resolved—all other efforts to overcome the difficulty having failed—to seek the sanction of the members of the Institute of Preventive Medicine to again change the designation, and to associate the Institute in future with the honoured name of Lord Lister. This was approved in August, 1903, and the title of "The Lister Institute of Preventive Medicine" was unanimously adopted. At the same time, with the sanction of the Jenner Memorial Committee, the sum that had been received by the Institute, referred to above, was applied to the foundation of a Jenner Memorial Scholarship at the Institute for scientific research on Jenner's own lines.

The permanent income of the Institute was not, however, adequate to the requirements and capabilities of the enlarged establishment, until towards the end of 1898 it received, for the encouragement of research into the cause and treatment of disease, a most generous endowment of a quarter of a million sterling from Lord Iveagh.

After this great gift some changes were made in the

executive body of the Institute, but the new governing body remained under the Presidency of Lord Lister, and the Council, though ceasing to be the directly administrative body, still continued to exercise an influence over the affairs of the Institute through the three members annually elected by it to the governing body.

By means of Lord Iveagh's gift the new governing body naturally found itself able to greatly increase the sphere of usefulness of the Institute and to make several important additions to the scientific staff.

About the same time the Great Central Railway acquired the Institute's premises at Sudbury. In their place the governing body was fortunately able to purchase near Elstree more suitable freehold premises, including about twenty-eight acres of pasture, and furnished already with several ranges of excellent stabling and other good buildings. To these have now been added a series of new laboratories designed with all the improvements which modern science can suggest, and the establishment, which is more fully described below, has the additional advantage of being in the open country and clear of other houses.

The general research laboratories and administrative offices of the Institute are situated at Chelsea. The building comprises bacteriological and chemical departments, and special laboratories set apart for cancer research and the chemical and bacteriological examination of water, together with the necessary accessories of a research institute. Here also a certain amount of diagnostic work is done for various sanitary authorities and other public bodies, but the ordinary chemical and pathological examination of material and the bacteriological examination of specimens for private practitioners being already well provided for, the Institute has no wish to undertake routine work of this kind. At the same time, where obscure or difficult

problems either in public or private practice arise, the Institute is prepared to render direct assistance or to act as referee should doubtful points be referred to it.

The water laboratory was established at the Institute by a further bequest from the trustees of the late Mr. Richard Berridge of £26,000. In this laboratory researches on the bacteriology and chemistry of water and sewage are conducted. The Institute has thus been enabled to devote special attention to the study of water problems in relation to hygiene, and has from time to time advised as to the character of water supplies, in fulfilment of the objects of the bequest. It is prepared to place the experience thus gained at the service of sanitary and other public authorities desirous of obtaining an opinion as to the quality of their water supplies, or confronted with outbreaks of disease supposed to be connected with those supplies.

SERUM DEPARTMENT.

The Serum Department of the Institute is at Queensberry Lodge, near Elstree, Herts, about three miles from Elstree Station on the Midland Railway. The buildings are on the summit of a small hill, and attached to them are about twenty-eight acres of grass land, and this again is surrounded on all sides by open fields. Queensberry Lodge itself has been retained practically as it was when the estate was acquired by the Institute, and is now used for the accommodation of the junior staff, administrative offices, etc. The Bacteriologist in charge lives in a separate house. The laboratories, which have been built by the Institute, are of the most modern type, with papyrolith floors with rounded corners, white glazed adamant walls with a dado of white tiles, and comprise:

Large Routine Laboratory.

This is a large room with both side and roof lights, fitted with centre and side benches, fume chamber, etc. It is used for the filtration of diphtheria toxin, chemical work, section cutting, and the usual laboratory routine, such as blow-pipe work, fitting-up apparatus, etc.

Two Private Research Laboratories.

Both these have a north-east aspect with large windows, and are very well lit. They are fitted with low benches for microscopical work, and with separate Hearson incubators, shelves for chemicals, media, etc.

The Serum Laboratory

is used for the filtration and storing of the various sera. The windows are of ruby glass, so as to ensure a non-actinic light. Two large ice-safes for the storing of the sera occupy the centre of the room. This laboratory is reserved entirely for serum.

The Hot Room

is a small room with double walls, the space between which is packed with asbestos. There are two doors, with a space between forming a small ante-chamber or "air-lock," which is entered before entering the hot room itself, thus preventing the inrush of cold air on opening the door. The walls are fitted with shelves from floor to ceiling, and by means of a gas stove and Roux regulator the temperature is maintained at body heat. The diphtheria bacillus is grown in flasks on these shelves for the production of diphtheria toxin.

The Engine Room

is fitted with a gas engine driving a large centrifugal machine and disintegrator, and also a Root's Blower, which supplies sterile air to the bottling room. There is also a water pump supplying a vacuum and high pressure air.

The Bottling Room

is reserved entirely for the bottling of serum. The windows are of non-actinic ruby glass and are air-tight. Before bottling is commenced the room is filled with formalin vapour, which is allowed to remain in the closed room all night. In the morning the formalin vapour is displaced by a current of air which is blown into the room from the Root's Blower in the engine-room. This air is sterilised before its entry by passage through a large

filter of sterile cotton wool. The current of sterile air is maintained throughout the process of bottling, entering the room through the filter, and passing out through the roof by an exit which has a cotton wool filter.

The Culture Medium and Sterilising Room

is provided with autoclaves, steaming apparatus, thermostats, and vessels for the preparation of bouillon. Here the various media required are prepared. This room communicates with the hot room by a small opening with double doors, through which the flasks can be passed after inoculation, without lowering the temperature by repeatedly entering the room.

The Glass-cleaning Room

contains a dry-heat disinfector for sterilising glass, a still, and separate sinks for the cleaning of used and unused glass.

An Isolated Laboratory

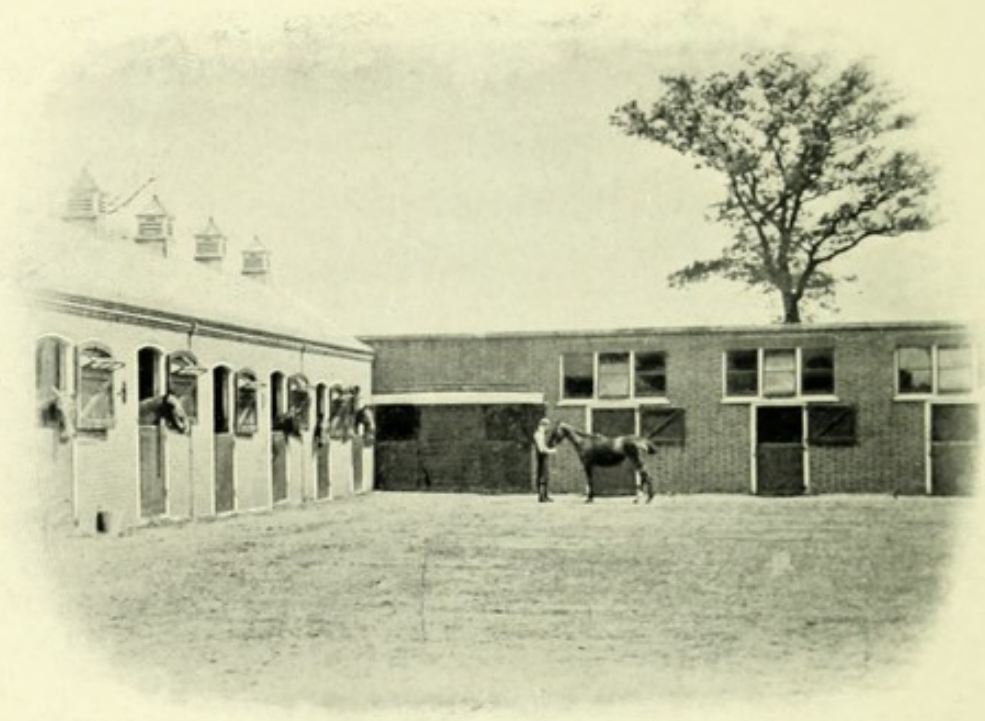
stands entirely apart from any other building. It is used for the preparation and filtration of tetanus toxin, and for the post-mortem examination of small animals.

The Animal Houses

are ordinary garden greenhouses, which have been adapted and prove excellent for the purpose, as they are easily kept at an even temperature. The larger is used as an experimental animal house for the housing of animals employed in the testing of the sera, toxins, etc. The roof is covered with vines, which have been retained as affording a shelter from the sun in summer. The two smaller houses are used for breeding purposes. The three houses are heated by a system of hot water pipes.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

A Laboratory at Queensberry Lodge.



Loose Boxes at Queensberry Lodge—Curiosity as to a New Comer.

The Principal Stables

form two blocks of builings about 200 yards from the laboratories. They are built of brick, upon the most modern type. There are two yards, the first of which is covered by a high glass roof, and opening from this yard is the operating room, where the horses are injected and bled. The stabling consists almost entirely of large, well-ventilated loose boxes, so that the animals have ample room to move about freely.

In the vicinity of the operating room is a small isolated room with slate benches where the blood-flasks are allowed to stand and where the serum is decanted.

There is a cottage for the head groom and quarters for the unmarried grooms, harness-room, coach-house, fodder-room, etc.

In one of the meadows, at a distance from the stables, is a loose box which is used as an isolation box. All new horses, undergoing a period of quarantine before being admitted into the stables, are kept under observation here. There are several other loose boxes in the meadows, as well as an isolated cow-shed, goat-house, pigeon-house, rabbit-runs, etc.

The department is under a mile from the nearest telegraph office, and is on the National Telephone Company's system. The various blocks are connected by inter-communicating private telephones.

Notes on Serum Therapeutics.

Many organisms, and notably those of diphtheria and tetanus, exercise their harmful influence by the secretion of a soluble poison or toxin, which is absorbed from the seat of infection and circulated in the body of the infected

animal. One of the means of defence against the invasion of such organisms which is possessed by the animal body is the capacity to manufacture, and set free in the blood stream, substances which combine with the toxins and so render them inert.

By habituating a large animal, such as a horse, to the action of the toxin in increasing quantities, some cells or fluids of its body can be thereby so stimulated to produce and put into the blood stream antitoxins in excessive quantity, that the serum of the animal may contain sufficient excess for its useful employment as a remedy for the disease in man or animals.

Von Behring must be regarded as the founder of serum therapeutics. In 1890 he, with Kitasato, showed that the blood serum of an animal which had been immunised against tetanus was capable, when injected into other animals, of protecting them not only against poisoning with tetanus toxin but also against infection with living tetanus bacilli. He also proved that, under certain conditions, a curative action could be demonstrated in animals which already presented symptoms of tetanus infection. Similar, though less striking, results were described in the case of diphtheria.

This work of Behring, though an epoch-making one, was not, however, the first suggestion that the serum of immunised animals contained substances which might be utilised for the protection and cure of other animals. Richet and Héricourt, in 1888, believed that they proved that the serum of a dog immunised against staphylococci protected rabbits against that infection.

Babes and Lapp, in 1889, showed that the serum of dogs immunised against rabies contained substances which, injected into other dogs, were capable of protecting them against rabies. But though the work of both

these authors contained the germ of the idea of serum therapeutics, neither in the clearness of the expression nor in the completeness of the demonstration did they approach the work of Behring, which, by the experimental proof presented, first impressed the scientific world with the greatness of the conception, and opened a door for further investigations.

At the Medical Congress at Buda-Pesth in 1894 Roux read a paper on the treatment of diphtheria by diphtheria antitoxin, which first proved to the medical world that this was the one method of successfully combating the disease. The experimental and clinical data, and the favourable statistics brought forward by Roux, at once put this method in a secure position from the practical standpoint.

The Preparation of Antitoxins.

For the preparation of antitoxins on a large scale the horse is the animal now almost exclusively used. The horse can be suitably immunised against tetanus, diphtheria, and other diseases, and the sera obtained are capable of attaining to a very high antitoxic value.

Precautions taken in the selection of the horses for the preparation of antitoxin.

The horses are selected by a skilled veterinary surgeon. They must be free from all signs and symptoms of disease. Every horse is tested for latent glanders with mallein, and even a suspicion of a reaction is regarded as a sufficient basis for the rejection of the animal. If the animal has satisfactorily passed the test he is received into the establishment, but is isolated and kept under observation

for some time. Under certain circumstances a second mallein test is carried out. Having passed through this period of probation the animal is admitted into the stables, and the process of immunisation is commenced. During the process the animal is kept under the strictest observation, his temperature is duly registered, and the greatest possible care is taken in regard to his comfort and feeding.

The Process of Immunisation.

The general principle is that the animal is treated with increasing doses of the particular poison. The toxins, which have been previously tested on small animals, such as rabbits and guinea-pigs, are injected subcutaneously, intramuscularly, or intravenously.

At first either very minute doses of weak toxins, or toxins which have been modified by chemical agents, or in other ways, are employed. In the case of tetanus, in the early stages the toxin is usually modified by being treated with iodine. The injection of the toxin may be followed by swelling at the site of inoculation, loss of appetite, general *malaise*, and rise of temperature. When these have passed off the animal receives a second, rather larger injection, and in this way the quantity of toxin is increased until within a few months the horse is capable of tolerating many thousand multiples of what would be a lethal dose if given as a first injection. When the serum has reached the strength suitable for clinical use, blood is withdrawn from time to time by venesection.

Antiseptic Precautions.

All the processes connected with immunisation are carried out under the strictest antisepsis. Syringes, needles, and instruments are boiled, and the blood is received into vessels which have been sterilised in the

autoclave at a temperature of 120° C. The skin of the horse is shaved and thoroughly cleansed with soap and water. The shaved area is then washed with a two per cent. solution of lysol, which is especially suitable for the removal of the oily substances from the horse's skin. It is finally washed with 1 in 1,000 corrosive sublimate solution.

Precautions employed in preparing the different sera.

The vessels containing the sterile blood are removed into a small isolated building used for this purpose only. The serum, when it has separated from the clot, is decanted into sterilised vessels, the usual bacteriological precautions being taken to prevent the admission of extraneous germs. In certain cases the blood is received into a special apparatus in which the fibrin is removed by whipping, the blood corpuscles being separated either by sedimentation or by the use of a centrifuge. To the serum thus obtained 0·2 to 0·3 per cent. carbolic acid is added. As a final precaution the serum is passed through a Berkefeld filter. It is then in a condition to be put into the small phials in which it is sent out for use. Before this is done, however, it is subjected to the following tests :

1. For sterility. It must be germ-free.
2. For absence of toxicity.
3. For antitoxic value. This must reach a required standard.

The last two tests are carried out on small animals. The serum is also kept for a certain time during which the horse remains under observation ; if during this time the animal shows any signs of illness the serum is thrown away.

Testing of Antitoxic Sera.

Several methods of testing the strength of antitoxins have been employed. The first methods consisted in ascertaining the exact dose of toxin, or of living culture, required to kill an animal such as a guinea-pig, of a certain weight, and pitting against this dose varying quantities of antitoxin.

With a single minimal lethal dose the results were irregular, and it was soon found more satisfactory to employ as the test dose ten times this quantity. By Ehrlich's older method of testing, ten times the amount of serum which protected a guinea-pig of 250 grams weight against a tenfold lethal dose was called one unit, i.e., an amount of serum capable of completely neutralising about 100 fatal doses of this toxin solution for a guinea-pig of 250 grams.

This method of standardising the serum, however, presented difficulties, for it was found that different solutions of toxin which were equally poisonous required quite different amounts of serum to neutralise them. Ehrlich afterwards discovered this to be due to the fact that a solution of diphtheria toxin undergoes certain changes by which it loses its lethal power without losing the power of neutralising antitoxin. On the other hand, diphtheria antitoxin, especially in the dried state and in *vacuo*, remains stable. Ehrlich, therefore, made his standard an antitoxin one. The unit he fixed on, while derived from the older method of testing, was to some extent an arbitrary one.

The bottles of diphtheria serum supplied by the Institute contain at least 2,000 of Ehrlich's units.

A living culture of a bacillus may be employed for test purposes. This method is still used by certain French workers. In the case of bactericidal sera it is a method universally employed.

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DIPHTHERIA.

In 1883 Klebs discovered the specific cause of diphtheria, and in 1884 Löffler succeeded in isolating the bacillus and growing it in pure culture. The bacillus is, therefore, known as the Klebs-Löffler bacillus. Roux and Yersin in 1888-1889 published important papers on the subject, in which they showed that the bacillus is capable of producing the various phenomena associated with the disease, including the formation of false membrane, and diphtheritic paralysis.

They also succeeded in separating and studying the toxin, which they found to be capable of producing all the effects produced by the bacillus. In 1890 appeared the great work by Behring, to which reference has already been made; and the observations in regard to diphtheria made in that work were extended and strengthened in a paper by Behring and Wernicke in 1892.

Curative Action.

By showing that the horse reacted to repeated and increasing injections of diphtheria toxin, by manufacturing and circulating in its blood such quantities of antitoxin that a few cubic centimetres of their serum was possessed of sufficient curative power to be useful in the treatment of diphtheria in the human subject, Roux and Ehrlich first brought the subject from the experimental to the practical stage; and since that time the results obtained

everywhere have proved the value of the antitoxic treatment of diphtheria.

It would be impossible here to enter fully into the statistics showing the enormous fall in the death-rate from diphtheria since the introduction of the antitoxin treatment, but the tables appended are of interest as illustrating the results obtained in this country.

Table 1.

Statistics of Cases of Diphtheria Treated in the Metropolitan Asylums Board Hospitals.

Year	Cases Treated by Antitoxin; per cent. of all cases	Mortality; per cent. of all cases
1888–93	—	28·5
1894	—	29·6
1895	61·8	22·5
1896	71·3	20·8
1897	80·2	17·5
1898	81·4	15·5
1899	—	13·95
1900	—	12·01
1901	—	12·5

From the above table it will be seen that the progressive fall in the death-rate corresponds with the increase in the percentage of cases treated.

Since the earlier works on the subject great improvements have been made in the technique of immunisation. One of the most marked advances has been in the direction of obtaining powerful diphtheria toxin, the first great essential for the production of powerful antitoxins. As a result of the advance of knowledge on this subject very powerful antitoxins are now obtained, a strength of over 1,000 units per c.c. being by no means infrequent. Although at the Lister Institute such antitoxins are not infrequently obtained, the serum is not sent out in different strengths at different prices, but a uniform strength in suitable volume for clinical purposes is fixed and supplied

Table 2.

SHOWING THE RESULTS OBTAINED BY ANTITOXIN TREATMENT ACCORDING TO THE PERIOD AFTER THE ONSET OF THE DISEASE AT WHICH THE INJECTION IS GIVEN (DIEUDONNÉ), DEMONSTRATING THE IMPORTANCE OF EARLY TREATMENT.

Author	Total of cases	Percentage of total mortality	First day	Second day	Third day	Fourth day	Fifth day	Sixth day	After sixth day
Welch	1,189	14·2	2·3	8·1	13·5	19·0	29·3	34·1	33·7
Hilbert	2,428	18·3	2·2	7·6	17·1	23·8	33·9	34·1	38·2
Collective Investigation of the American Pædiatric Society ..	5,794	12·3	4·9	7·4	8·8	20·7	35·3	—	—
Collective Investigation in Austrian Sanitary Department	1,103	12·6	8·0	6·6	9·8	25·5	28·8	30·7	21·0
Collective Investigation of the Imperial German Health Office	9,581	15·5	6·6	8·3	12·9	17·0	23·2	—	26·9

at one price. The bottle of antitoxin in each case contains at least 2,000 units.

Dosage.

Great difference of opinion still exists as to the suitable dosage of the antitoxin. The bulk of opinion now seems to be that for moderately severe cases, whether in adults or children, a dose of 2,000 units is sufficient, and for a very severe case 4,000 units. It is pretty generally agreed that it is more efficacious to give one large dose as early as possible in the disease than a number of small doses at intervals. Intravenous injection in severe cases has also been recommended. Behring says that by this method a gain of eight hours may be obtained. Only antitoxins free from antiseptics should be employed for intravenous injection, and care should be taken to avoid any precipitate which may have settled at the bottom of the flask.

One of the most important conditions of success in the treatment of diphtheria with antitoxin is that the antitoxin should be injected early. This is very clearly brought out in the statistical tables appended; the first of which shows the collected experience on the subject, the second the experience at the Brook Hospital of the Metropolitan Asylums Board.

Table 3.

Showing Percentage Mortality at the Brook Hospital during 1901, and the results obtained from the injection of Antitoxin on the different days of the disease.

Day of Disease	1st	2nd	3rd	4th	5th and subsequent
No. of Cases	38	170	192	137	186
Percentage Death-Rate..	0·0	4·1	11·9	12·4	16·6

Dr. MacCombie states that at this Hospital, during five consecutive years, there has not been a death among the cases that came under antitoxin treatment on the first day of the disease, and that during the same period among cases treated on the second day the death-rate has not exceeded 5·4 per cent.

From this may be deduced the rule to inject the antitoxin as early as possible. Time must not be lost by waiting for the bacteriological report which may be necessary to confirm the clinical diagnosis.

Prophylactic Action.

Hitherto in England diphtheria antitoxin has not been much used as a prophylactic, though in certain outbreaks, such as those at Cambridge and Chesterton, it was employed with considerable success. In France, Germany, and America, however, very valuable results have been obtained in this direction. The experience obtained in the clinics of Baginsky and Heubner in particular confirms the value of the antitoxin as a preventive.

It may be interesting to note here an experience which occurred in Heubner's clinic. From 1895 onwards prophylactic injections were given every three weeks to all the patients, and the outbreaks of diphtheria which had formerly regularly occurred in the wards came to an end. In October, 1897, this precautionary measure was stopped in a wing not used for infectious cases, and in November cases of house-infection broke out in this department. A general prophylactic inoculation was again carried out, and the occurrence of cases completely stopped.

Such prophylactic injections are especially recommended in large families and schools should an outbreak occur.

Prophylactic Dosage.

250 units are sufficient for this purpose, that is to say, a single dose of 1 c.c. of the antitoxin as sent out by the Institute.

Site of Injection.

The flank between the crest of the ilium and the last rib and the lower part of the abdomen are generally selected, but any region with loose subcutaneous connective tissue is suitable. The injections should be subcutaneous.

Antiseptics.

In performing the injection strict antisepsis must be observed. The syringe must be well washed and boiled before use.* The skin must be well cleansed with soap and water, and afterwards treated with an antiseptic such as a 1 in 1,000 corrosive sublimate solution, or 1 in 20 carbolic acid solution.

TETANUS.

The tetanus bacillus was discovered in 1894 by Nicolaier. Kitasato, at a later period, obtained pure cultures, which he proved to be capable of causing the disease in animals. As already mentioned, the same worker, along with Behring, first succeeded in obtaining tetanus antitoxin.

Curative Action.

It is possible to obtain antitoxin of extraordinary preventive power, as tested experimentally by injecting the serum previously to the toxin. The experimental results

* A syringe with asbestos plunger, which can easily be taken to pieces and boiled, is described on page 30.

A Private Laboratory at Queensberry Lodge.

THE RESIDENCE OF THE JUNIOR STAFF, QUEENSBERRY LODGE.

are equally as satisfactory when the two are mixed together at the time of injection, but as a curative agent its power is far less than that of the corresponding antitoxin for diphtheria, because the disease is usually only discovered after serious lesions of the nervous system have already been produced, over which, unfortunately, the antitoxin can exert little influence.

At the same time it must be remembered that even after symptoms have appeared toxin still circulates in the blood, or may still be in process of formation at the site of infection. There is no doubt that the injection of antitoxin can neutralise this free toxin and combine with any toxin which may be produced after its injection. Though it cannot restore damage done to the nervous elements it may prevent further nervous elements from being attacked.

Koehler dealing with the statistics of ninety-six cases treated by antitoxin found the death-rate to be 30·4 per cent., which is certainly much below the normal death-rate, viz., 86 per cent. On the other hand, Steuer from his statistics could demonstrate no improvement over cases treated without antitoxin. Only time and further observations can decide the value of the method.

Dosage.

Five injections in separate situations (in all 100 c.c.) should be made subcutaneously at once, and be repeated on the two following days, and a final injection should be given, even in favourable cases, ten to fourteen days after the first injection.

Intravenous and intracerebral injections have also been recommended.

The intracerebral injection of serum, recommended by

Roux and Borrel, gives, with guinea-pigs, curative results superior to any other method.

If intracerebral injection is employed on the human subject, a serum free from all antiseptic, and so powerful that a dose of 2 to 3 c.c. is sufficient, must be used. Antitoxin for this operation is prepared, without the addition of antiseptics, at the Institute. Hence, in applying for the antitoxin, the purpose for which it is intended to be used ought to be stated.

Dosage for Horses.—Behring recommends the same quantities as are used for man.

Prophylactic Action.

Whatever doubts may be entertained of the value of this antitoxin as a curative agent, as a prophylactic agent its power is fully established. In veterinary practice, where it has been used under test conditions, it has proved almost infallible. Nocard has collected the results of the experience of prophylactic injections gained by sixty-three veterinary surgeons during a period of twenty-two months.

2,700 cases, both operative and traumatic, were selected from those in which by experience they knew that tetanus was most likely to occur. Not one of these 2,700 animals died of tetanus, whereas in the practice of the same veterinary surgeons, during the same period, but not so treated, 259 cases of tetanus occurred.

In case of severe wounds, such as compound fractures, where there has been much soiling of the wound, and especially if earth has found its way into the depths of the wound, a prophylactic injection of tetanus antitoxin is strongly indicated.

In severe shell wounds in time of war, and where the

wounded have been lying for any time in contact with the earth, a prophylactic dose, 20 c.c. subcutaneously, would be advantageous.

STREPTOCOCCUS INFECTION.

The streptococcus pyogenes is the most important causal organism in septic infections such as acute abscess, erysipelas, and puerperal septicaemia.

There is great difference of opinion as to whether all these streptococci belong to one species, or whether there are streptococci which, though morphologically and culturally indistinguishable, are yet not identical. Around this question hinges one of the great problems of the serum therapeutics of such conditions.

Marmorek first succeeded in obtaining antistreptococcic serum. In immunising the horses, he used cultures of streptococci which had been elevated in virulence by passage through rabbits.

The sera of diphtheria and tetanus owe their action to their "antitoxic" properties. In the case of the anti-streptococcic serum the active agent is little, if at all, due to an antitoxin, but to "antibacterial" substances, which occasion the death and destruction of the organisms.

Van de Velde showed that the serum of the horse, prepared by injecting one streptococcus, would protect rabbits against that particular streptococcus, but not against certain other streptococci. The contradictory clinical results obtained with the serum may be largely

due to this circumstance. To obviate this difficulty he suggested that a large number of races of streptococci should be used in immunising the horses, and thus a "polyvalent" serum be obtained. The antistreptococcic serum supplied by the Lister Institute is a polyvalent, one prepared in this way.

Although the experimental results are not at all on the same level as those obtained with diphtheria and tetanus, the evidence is in favour of the serum having protective and curative powers. It is also difficult to explain many of the clinical results in any other way than by attributing the favourable issues recorded to the use of the serum.

Dosage.—30 c.c. should be given at once in an acute case, and repeated daily until improvement is marked. Local injections into the primary focus are indicated

AFTER-EFFECTS ASCRIBED TO, OR CAUSED BY, SERUM INJECTION.

Rashes.

Although rashes may occur in diphtheria and other toxic and septic diseases where no antitoxin has been used, there is no doubt that the serum treatment is the cause of a large number of rashes. The production of a rash is not due to anything connected with the immunisation, or to the anti-bodies in the serum, but is due to something inherent in the serum of the horses and other animals, for the injection of a serum from a normal healthy horse may be followed by rashes. These rashes may be accompanied by slight rise of temperature. Beyond this, and the nervous irritation produced by their presence, they cause no bad after-effects.

The commonest forms of these rashes are urticaria, erythema, and scarlatiniform eruptions.

These occur from four days to five or six weeks after the injection; they are commonest from the eighth to the fourteenth day.

Arthropathies.

Joint pains, which may affect one or more joints, accompanied in certain cases by stiffness, slight swelling, and neuralgia, are much rarer after-effects than the skin eruptions. They occur usually at the same time as these,

and like them are due to something inherent in the serum of particular horses. This condition of the joint never goes on to suppuration. As a rule it disappears in a few days, though rarely it may persist for a few weeks.

Diphtheritic Paralysis.

The increased number of cases of paralysis following the use of antitoxin has by certain individuals been attributed to the use of antitoxin. Experimentally it has been shown that the antitoxin, if given early enough, protects against the paralysing substance. The increase in the number of such cases must, therefore, be attributed to paralysis occurring in cases which, had antitoxin not been used, would have proved fatal in the early stage of the disease.

STORAGE OF ANTITOXINS.

The cases containing the antitoxin should be kept in a dry, cool, dark place. When kept under these conditions there is little deterioration in their therapeutical value. Sufficient excess is added to each bottle to compensate for any loss in antitoxic value which might occur during at least one year.

Stable Yard at Queensberry Lodge.

Stables and Paddocks, Queensberry Lodge.

TUBERCULIN AND MALLEIN FOR VETERINARY USE.

Tuberculin and mallein are prepared at the Lister Institute from fluid cultures of the tubercle bacillus and the glanders bacillus respectively.

The cultures, after sterilisation at boiling point, the bacilli being killed by boiling, are passed through a Chamberland filter, and in this way the dead bodies of the bacilli are removed from the fluid in which they are grown.

The clear filtrate obtained is concentrated on a water-bath. The syrup-like fluid resulting constitutes the crude tuberculin and mallein, and consists essentially of certain proteid constituents of the organisms along with any products of their growth that may be present in the culture medium.

These substances on injection produce a peculiar reaction in the bodies of animals suffering from tuberculosis or glanders, characterised by a certain rise of temperature above the average normal, varying from about 2° to 5° F.

Tuberculin and mallein so prepared are not supplied for curative purposes. Their main value lies in the means they afford for the detection of latent tuberculosis or glanders in the lower animals in the hands of the veterinary profession. They are, therefore, supplied for use as diagnostic agents.

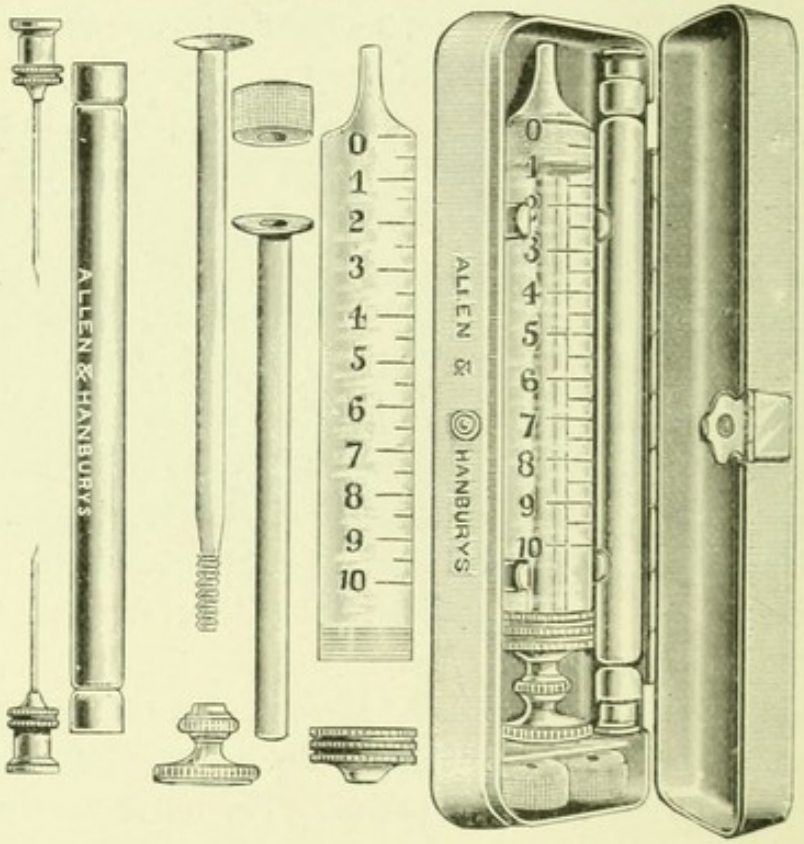
The tuberculin and mallein issued consist of the crude tuberculin and mallein diluted by the addition of a half per cent. watery solution of phenol. The full instructions as to their use and the interpretation of the results obtained are given with each bottle. It is recommended that the dilute tuberculin and mallein be kept in a cool and dark place, and that they be used within fourteen days of their

receipt. In the event of these agents being required for use abroad, it is advised that they be obtained in the concentrated form and the requisite dilution made immediately before use. The injections should be carried out with aseptic precautions.

Neither tuberculin nor mallein can in any way convey tuberculosis or glanders to the animals tested, inasmuch as the specific infective agents in each case have been killed by heat and removed by filtration from the fluid.

ANTITOXIN SYRINGE

CAPACITY 10 CUBIC CENTIMETRES.



In Nickel Plated Metal Case, with Needles in a Metal Protecting Tube.

The syringe is made with an asbestos plunger, and is easily taken apart, as shown, for the purpose of sterilising.

INDEX.

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