are perhaps most noticeable when given in combination with acetate of potash, digitalis, and squill. Diuretin, again, is a remedy which we could ill spare. It is most useful in cases where digitalis has failed to bring relief or could not be taken without unpleasant effects. The drug has little or no action upon the cardiac muscle and appears to exert its influence as a diuretic quite apart from any increase of the blood pressure. It may therefore be given without misgivings when blood pressure is high and when, as a consequence, digitalis and other cardiac tonics are not desirable remedies. Diuretin has been found of especial value in cases of acute cardiac dropsy where the symptoms appear very suddenly. It may be usefully combined with infusion of broom-tops and small doses of tincture of strophanthus.

Some cases of cardiac dropsy resist treatment with extreme obstinacy. Although the diet may be arranged carefully both as to quantity and quality and the bowels kept regular and free, the patient seems to be unable to respond satisfactorily to any treatment, and meets every fresh combination of diuretic remedies with the same disappointing insensibility. When progress seems thus at a standstill, there are two drugs, either of which will often bring about a welcome change in the situation. One of these is tincture of cantharides. I look upon this remedy as one of our most useful means of promoting diuresis in cardiac dropsy. Its action is upon the secreting cells of the tubules, and the effects manifest themselves very quickly. I have often seen a formidable quantity of fluid disappear in the course of a few days under the influence of this remedy, although all previous treatment had failed to make any impression upon the complaint. The dose may be 2 or 3 to 10 minims, according to the age, given several times a day. The tincture can be used in combination with any other remedy, and may be usefully added to a mixture containing caffeine, tincture of strophanthus, and spirits of nitre.

The other remedy which in obstinate cases can often be given with conspicuous success is mercury. Either calomel or blue pill may be employed, but I prefer the latter. This remedy is well known as a useful addition to digitalis and squill when these drugs are prescribed for their diuretic action, but it is when given alone that the effects of blue pill are most strikingly manifested. The cases which are best fitted for this treatment must be chosen with care. The drug seems to have an action complementary to that of digitalis, and to prove most efficient in cases where the latter has failed to increase materially the urinary secretion. It may therefore be regarded as belonging to the same group as diuretin and caffeine. Mercury is to be avoided if renal disease be present, and when given should not be pressed if diuresis do not result in the course of three or at the most four days, for it is in such cases that the system may possibly be unfavourably affected by the treatment. I have given blue pill in doses of 3 grains three times a day in many cases, both to young people of 10 or 12 years of age and also to the adult, and have found it to be very well borne and produce free secretion; but when diuresis has been fully established I have made it a rule to discontinue the mercury and replace it with a mixture of caffeine and spirits of nitre with infusion of broom-tops. If the mercurial be continued too long we run the risk of setting up stomatitis; and in any case it is wise while the remedy is being taken to wash out the mouth several times a day with a suitable antiseptic solution. The drug is supposed to act by increasing the formation of urea, which is well known to have a powerful diuretic action, or possibly it may directly stimulate the renal cells. The mercurial treatment should be reserved for cases which have proved obdurate to other methods, and it is fortunately in just such patients that the most successful results have been observed.

Messrs. S. F. Edge, Limited, have issued a catalogue of their 1911 noiseless Napier cars. Special attention is called to the colonial Napier models, which are built to suit the varied requirements.

The International Exposition of Food, Brewing, Wines, Liqueurs, and the Industries relating thereto, with a section of medico-pharmaceutical hygiene, is to be held at Antwerp this year. The exposition will be open from September to November. It is under the patronage of Her Royal Highness the Countess of Flanders.

ON SOME POINTS CONNECTED WITH THE SERUM TREATMENT OF DIPHTHERIA.*

BY

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The serum treatment of diphtheria has now been in the hands of the profession for so long a period—namely, upwards of sixteen years—that it may possibly be a matter of surprise to some that it should be chosen as the subject for discussion now. I understand, however, that there are special reasons for this choice. Hitherto, in London at any rate, the serum treatment of diphtheria amongst the poor has been almost entirely confined to hospital practice. Partly because the medical practitioner knows that if he notifies a poor person to be suffering from diphtheria, the patient will speedily be removed to hospital, there to receive appropriate treatment, and partly because, even if he wishes to make use of serum before the removal of the patient, he is deterred by the expense of the remedy, it is rarely that a patient is treated with antitoxin before he is removed to hospital. There is no doubt that any considerable delay in the employment of antitoxin in the treatment of diphtheria is highly detrimental to the interests of the patient. In order, therefore, that the poor patient may be subjected to the most efficacious treatment at the earliest possible moment, even before removal to hospital, the Local Government Board on August 15th last issued an Order sanctioning the provision by the councils of the metropolitan boroughs of a temporary supply of diphtheria antitoxin. I understand that the City of Westminster is proposing to avail itself of this Order and to supply medical men residing in that city with antitoxin for use in suitable cases. This action of the public health authority may result in forcing the serum treatment of diphtheria upon the notice of some who have not up to the present been practically concerned with it. In complying with the request of the Executive Committee of your Division to read this paper I take the opportunity of bringing forward certain points connected with the antitoxin treatment which do not appear to be generally known.

I wish, in the first place, to make it quite clear that I am myself most firmly convinced of the value of antitoxin in the treatment of diphtheria. I have had an extensive experience of the disease reaching back to eight years before the discovery of the serum method, and I regard the antitoxic serum as a specific. But at the same time I am of opinion that there are certain limits to its use, and what they are I shall presently indicate. Another point I am also quite decided upon, and that is the importance of early treatment. As I am so certain upon these two points it may be said to me that the only limit to the use of antitoxin is the limit of dosage—that if a person is suffering from diphtheria, or is suspected to be suffering from diphtheria, he should have antitoxin. That is a view I myself held some years ago, but a more extensive experience has led me to modify it. I think that the most convenient course I can take in this paper is, first, to give the reasons for the modification which I have deemed it desirable to make in my opinion and therefore in my practice, and, secondly, to point out in what these modifications of practice consist.

Serum Sickness.

Immediately after the introduction of the serum treatment of diphtheria in 1894 it was observed that in a certain number of the patients treated symptoms appeared of such a nature as very rarely indeed occurred in diphtheria cases not treated with serum. It soon became clear that these symptoms were due to the serum. As serum treatment was extended to other diseases—such as tetanus, streptococcal infection, and enteric fever—it was found that the symptoms alluded to were not due to the antitoxic or antimicrobic principle in the serum, but to the serum itself. Serum from a horse which had not been immunized against any disease was found to produce these

* A paper read before the Westminster Division of the Metropolitan Counties Branch of the British Medical Association.

symptoms in a certain number of persons. The symptoms are fever and a rash, usually urticaria or a variety of erythema multiforme. These symptoms occur in about 33 per cent. of the cases treated. But, besides them, other and much more unpleasant symptoms were observed, though less frequently, in 3 or 4 per cent. of the cases—namely, acute pains in joints, tendons, and fasciae, with fever. Occasionally the joints were swollen. There was, in fact, arthritis. In such cases the symptoms bear some resemblance to an attack of rheumatic fever. I need hardly say that an attack of this kind is most unpleasant. It was recognized at the time that this added illness might act prejudicially on a patient who was just recovering from a severe attack of diphtheria, but it was felt that the risk of harm from the "serum sickness"—to use the expression of von Pirquet and Schick[1]—was less than that which was incurred if the patient was left to the mercy of an attack of diphtheria. One other observation was made in respect of these symptoms, the significance of which will appear later—that they rarely set in before the expiration of a week from the injection of the serum—that is to say, after what might be called an incubation period of some duration, which in some instances is prolonged to as long as even three weeks.

This febrile attack, with a rash and in some cases also with arthritis, constitutes what has been termed the "normal reaction" due to horse serum. As the horse is the animal which is almost solely employed for the production of the various curative serums, our knowledge of the serum sickness is almost entirely derived from the use of horse serum. But it is known that the serum of other animals will give rise, more or less markedly, to the same effects.

As I have said, the relation between the sickness and the serum was recognized as soon as the antitoxin treatment was in full swing. In the vast majority of cases the sickness, though it may be unpleasant, is not dangerous; and the normal reaction has come to be looked upon as a minor evil that has to be put up with.

Abnormal Reactions.

Besides the normal reaction there are other reactions due to serum, which have been called "abnormal reactions," because they differ very widely in their appearances from the normal reaction. In some cases the difference is rather one of degree than kind; but in others the phenomena are totally different from those of an attack of ordinary serum sickness. It was some time before these abnormal reactions were recognized and the circumstances under which they arose defined. They may be divided into two main classes—the one in which the patient has previously been injected with serum, the other in which he has not.

Abnormal Reaction after Second Injection.

The first class may be subdivided into three groups.

The first, in which the symptoms appear after the usual incubation period of not less than one week, but they are unusually severe, and occasionally a symptom not seen in an ordinary attack of serum sickness is met with. The following is an example of this form of abnormal reaction. I select this instance—as I shall later select other instances—because it happened to and is related by a medical man, who is able to describe the symptoms much more graphically than could be delineated by the mere passive observer. Dr. W. Bligh[2] was led to relate his own "tale of woe" by the publication of a somewhat similar tale by Dr. R. Thorne Thorne, whose account of his own case I shall presently read to you.

About four years ago I gave myself a prophylactic dose of antidiphtherial serum of 1,000 units in the left forearm. Nine days after an urticarial rash appeared all over the left upper extremity, but nowhere else. It disappeared within a day or two.

You will notice that after that injection Dr. Bligh suffered from a mild attack of ordinary serum sickness.

Eighteen months ago I again gave myself a similar dose, in the same place. On the evening of the ninth day, after dinner, I suddenly came out in an urticarial eruption over the left arm, front of chest, and abdomen. The rash appeared literally in a few minutes, and was very profuse. I walked from my drawing-room into my study, a distance of a few paces, to consult Dr. Kanthack's article in Professor Sir Clifford Allbutt's *Medicine* on the subject. Before I found the reference the rash disappeared, and I was immediately seized with such faintness that I had to lie prone on the floor. In a few minutes I had sufficiently recovered to crawl upstairs on hands and knees and climb into bed. *Pari passu* with this improvement of feeling out came the urticarial rash once more all over my body, on the abdomen and thorax the wheals being as large as a good-sized plate. In a few minutes more the lips and buccal surface of the cheeks began to swell, and a most uncomfortable feeling behind the sternum and in the epigastrium became noticeable, suggesting that the oesophagus and stomach were taking part in the orgy. I passed a most unhappy night, no vomiting, like my brother sufferer, Dr. Thorne Thorne, but a continued misery of feeling that the post-sternal and epigastric pain would go if I could only bring up flatus. However, between 3 and 4 a.m. the discomfort abated, sleep came, and I awoke later in the morning feeling quite well, with the rash gone, and able to do my day's work as though nothing had occurred.

On this occasion Dr. Bligh suffered from a much more severe attack of serum sickness, and the symptoms were unusual in that they came on very abruptly, the rash invaded the mucous membranes, and there was faintness. But the incubation period was present, and was of customary duration.

In the second group the symptoms may or may not be of extraordinary severity or character, but the characteristic feature is that, while there is an incubation period, its duration is shorter than usual. Instead of being seven days or more it may be twelve hours to six days. This is the "accelerated reaction" of von Pirquet and Schick. The following is an example of this reaction.

Louisa C., aged 6 years, received 12,000 units of antitoxin for an attack of diphtheria. This was followed by a slight rash four days later,* and by a second rash, fever, and joint pains on the ninth day from the injection. Some weeks later the child had a relapse of diphtheria, and she was again treated with antitoxin, 6,000 units of which were given 109 days after the first injection. The next day an erythematous eruption made its appearance, which lasted for several days and was accompanied by sharp febrile symptoms, the temperature being 104° F. and 105° F. on the fourth and fifth days of the rash.

Another and more severe instance of the accelerated reaction is the case of Dr. R. Thorne Thorne,[3] which I now relate in his own words.

I suffered from a mild attack of diphtheria in 1889, followed by a troublesome paralysis, and hence I have since on three different occasions injected myself with a prophylactic dose of the serum (1,000 units) when attending cases of diphtheria in which I have been more than usually exposed to a virulent infection. My first injection was in December, 1902, after which I suffered from a slight urticarial rash round the seat of injection. My second was in September, 1904. This was followed by a more general rash and some malaise. My last injection was in November, 1907. Two days after the injection I felt very unwell; three days later I could hardly do my work as I felt so ill, and my suboccipital lymphatic glands were enlarged and tender. On the night of the seventh day I went to bed with the intention of stopping there next day, as I felt unfit for work, and was suffering from a more or less generalized urticaria. At 12.30 a.m. I awoke feeling sick, and vomited almost continuously for half an hour, till I was quite exhausted. The rash by this time had become general, and on the abdomen was in places quite the size of a five-shilling piece, and raised nearly half an inch. I was completely covered from head to foot with the exception of the palms and soles. The irritation was almost unbearable. At 3 a.m. I was again seized with vomiting, which lasted quite half an hour. By this time my tongue had swollen, due to the urticaria, and I found some difficulty in breathing. At 4 a.m. the joints below the hip and shoulder were attacked, and became so swollen that I could not bend my fingers. By 8 a.m. the rash had almost gone, and I felt better, but on getting out of bed I found that I could not stand, and fainted. By the evening I felt well, but very shaken and weak. My temperature was normal during the week preceding the attack. I know that I had eaten nothing which could have upset me, and I believe that the vomiting was due to urticaria of the stomach. I also experienced some thoracic and abdominal pain during the height of the attack.

The characteristic feature of these two cases is that the symptoms of serum sickness began to show themselves earlier than usual, within twenty-four hours in the case of the little girl, and two days after the injection in that of Dr. Thorne Thorne. It will be noticed that Dr. Thorne Thorne suffered from faintness, and that his attack was much like that experienced by Dr. Bligh.

In the third group the symptoms of the serum reaction occur within a few minutes or five or six hours of the injection of serum. This is the "immediate reaction" of von Pirquet and Schick. In my experience I have only once known the symptoms of a serum reaction to appear

* Occasionally the incubation period of a normal reaction is less than a week.

between the sixth and nineteenth hour after an injection—that is to say, that an immediate reaction occurs within six hours of the administration of serum, and an accelerated reaction after a lapse of about eighteen hours. In one case a reaction which I regarded as accelerated occurred twelve hours after an injection. The symptoms of an immediate reaction are prone to be severe and even dangerous, and to be different in their character from those of the other reactions. The following is an instance of this reaction.[4]

"Elsie E., aged 3 years, suffering from a severe attack of diphtheria, received by subcutaneous injection 4,000 units of antitoxin on each of the days October 26th, 27th, and 28th, and 2,000 on the 29th, 14,000 units in all. A slight erythematous rash came out on November 20th, and lasted for three days. On December 14th symptoms of a relapse of diphtheria set in, and the next day, that is, fifty days after the first injection on October 26th, 4,000 units were injected beneath the skin. Within a quarter of an hour the child was very sick, and was covered with an urticarial rash. Two and a half hours later she had a rigor which lasted about half an hour. She became cyanosed, and the pulse was rapid and feeble. She gradually recovered though the rash was present the next day. A second rash made its appearance on December 21st and lasted to the 23rd, during which time the patient also suffered from fever.

The symptoms of the immediate reaction differ from those of the other reactions which I have described in their severity and the explosive suddenness with which they show themselves. Besides the rash—which may invade the whole of the skin, and, it would seem, certain of the mucous membranes also, in a very few minutes—there are a high temperature, cyanosis, and a rigor. Occasionally there is collapse, and in one case under my care there were convulsions and drowsiness.

Now, in each of these three groups of cases the peculiar symptoms manifested themselves in consequence of an injection of serum given for a relapse of diphtheria some considerable time after the first administration of serum. I drew your attention to the fact that an attack of serum sickness was preceded by an incubation period of about seven to fourteen days' duration. It is the merit of von Pirquet and Schick to have pointed out that an abnormal reaction did not occur in these cases of second injection, unless the second injection was given after the lapse of a period from the first injection which was longer than, or at least as long as, the ordinary incubation period—that is to say, at least a week. These reactions are not set up by a second, third, or later injection, unless there is an interval of at least a week between the first and the one that produces the abnormal reaction. The shortest period that I have observed for an accelerated reaction has been eighteen days, which is, I believe, the shortest recorded, while the longest has been 1,851. Von Pirquet and Schick have reported an interval of seven and a half years. The extremes for the immediate reaction that have been observed in my cases have been twenty-one and four hundred and thirteen days, but Currie[5] has reported a minimum of ten days, and von Pirquet and Schick a maximum of three years. It is quite possible that there is no limit to the maximum period, and that an abnormal reaction may be set up, in a person who has once been injected, by reinjecting him subsequently at any time. There are many cases on record in which reinjections have been practised at short intervals, but the cases in which the interval between the two injections is long are few in number.

From the clinical evidence I have brought before you, it is clear that the injection of serum into a human being may produce some changes in the blood or tissues, or in both, which may lead to a modification of the form of the serum sickness or reaction. The reaction is usually hastened; it may be severe, and in some cases uncommon symptoms are present. But, fortunately, it is not in every case in which reinjection is performed after an interval of some duration that these abnormal reactions occur. During the eleven years, 1897 to 1907, there were 164 cases of this kind of reinjection under my observation; of these, 27 showed marked and 51 less marked reactions. A considerable number of similar cases have been reported in various medical journals.*

In a certain number of persons, therefore, the injection of a foreign serum leads to an increased susceptibility or supersensitiveness to the serum, a condition which is shown by the greater readiness of the reaction to appear and its greater severity. In consequence of the occurrence of these abnormal reactions in persons treated with antitoxin and of certain still more serious results, to which I shall presently refer, the subject was specially investigated by bacteriologists and physiologists in the United States, though it had been inquired into previously by certain Continental physiologists who were engaged in researches into the causes of immunity. A vast amount of experimental work has been accomplished as a result of these investigations, and from it one fact emerges quite distinctly, and that is that if you inject a foreign protein into an animal you render the animal peculiarly sensitive to that particular protein. By "foreign" I mean not derived from the animal injected or one of its species. The protein may be of any kind and of animal or vegetable origin, such as, for example, blood serum, white of egg, milk, and bacterial extracts. In some animals and with some proteins supersensitiveness is produced with remarkable ease. Thus, the injection of $\frac{1}{1000}$ c.cm. of horse serum into a guinea-pig renders the animal so extremely sensitive that the injection of 3 c.cm. or 4 c.cm. a fortnight or more afterwards will almost invariably cause the rapid death of the animal. The condition of supersensitiveness thus produced has been termed by Richet, one of the earliest workers at the question, "anaphylaxis," meaning the opposite to protection. The animal, so far from being protected against the foreign protein, is very much more susceptible to its action. As I am this evening dealing with the subject only from a practical standpoint, I shall not enter into any discussion of the hypotheses that have been put forward to account for the production of this condition, which is possibly a stage in the acquirement of immunity.

*I have not included amongst these 78 cases of abnormal reaction any in which the signs of the reaction were limited to the site of injection.

Abnormal Reaction after First Injection.

So far I have been talking only about the first of the two classes into which I said the abnormal reactions might be divided—namely, that in which the patient had been injected with serum on a previous occasion. I now pass to the second class, in which an abnormal reaction follows a primary injection.

Now I said before that an ordinary attack of serum sickness did not as a rule come on till a week or more after the primary injection. Occasionally it may arise earlier, but if it does it is not necessarily severe or exceptional. But in the cases I am now about to speak of the symptoms are of a different character and alarming gravity. Again I will avail myself of the description given by a medical man of his own case and take that given by Dr. Arent de Besche,[6] who was the patient.

A medical man, 30 years of age, went on Sunday evening, December 5th, 1908, to visit a patient who was suffering from an affection of the throat, which was strongly suspected of being diphtheria. During the examination the patient coughed straight into the face of the doctor, and the circumstances of the place were such that the latter was unable to wash or disinfect himself till he reached home, nearly an hour later. The next day the diagnosis of diphtheria was confirmed bacteriologically, and the doctor, being persuaded that he had in all probability been infected with diphtheria, decided to have a prophylactic injection of serum. He received from one of the medical staff of the department of infectious diseases of the Municipal Hospital in Christiania an injection of 1,000 units of antitoxin in 2 c cm. of horse serum—a dose which is often given to the smallest child, and is only a fraction of the amount which is given to adults. The injection was made in the right side of the abdomen at the level of the umbilicus, and it is quite certain that no air was also injected. It should further be noted that before the injection the patient was in perfect health and had never before in his life been injected with serum. The injection was given at 1.30 p.m., and the patient immediately left the hospital to go home. He had hardly been gone five minutes when he began to feel an intense irritation in the nose and eyes, and sneezing came on so severely that he had to be constantly using his handkerchief. Shortly afterwards he began to cough, and ten minutes later urgent dyspnoea set in, with wheezing in the chest, just as in an attack of asthma. The dyspnoea rapidly increased, the respiration became stertorous, and the patient quickly became so helpless and ill that he was on the point of falling. He was obliged to appeal for help to the first passer-by in the street, and, with the aid of two men, was taken to one of the tram waiting-rooms and laid on a bench. Then there came on extreme breathlessness, pronounced lassitude, and a sensation of dissolution. The patient shivered, and his lower extremities, as well as his arms and hands, were cold. His hands were also extremely cyanotic; he

could not feel his pulse. After some time he was taken home in a carriage and was placed, in a helpless condition, on a sofa.

A doctor was sent for; Dr. H. J. Vetlesen attended, and the following notes were made by him:

I arrived at 3 o'clock—an hour and a half after the patient had been injected. The patient was lying, fully clad, on a sofa. His face, lips, cheeks, and ears were extremely cyanotic, and his hands were also in the same state. He was restless, and kept tossing himself from one side to the other and rubbing his back and abdomen with his hands; he was breathing heavily; the respirations were laboured, not wheezy, but stertorous. The patient gave me the impression of being in a very feeble state; his nose was stopped up as by a catarrh; he was constantly using his pockethandkerchief, and had used three in a short time. His hands were cold; his face, though cyanotic, was warm. His pulse could not be felt. It seemed to me that the patient was too weak to sit up, so that a thorough physical examination could not be made. . . . The sounds of the heart were audible and clear.

The patient gradually recovered, the only fresh symptom being irregularity of the pulse. By 8 p.m. he felt quite well again. He passed a good night. Next day there was redness and swelling round the site of injection, which spread to the loin and scrotum, and caused some annoyance. This lasted for three days.

Dr. de Besche got off lightly; for unfortunately there are several cases on record which have terminated fatally. The following is one such, reported by Dr. Gillette[7]:

The patient was a man 52 years old, who was the subject of asthma. Dr. Gillette states: "He asked me to administer diphtheria antitoxin to him, hoping it might cure his asthma. . . . On November 8th, 1907, I administered 2,000 units of antitoxin globulin under the left scapula, taking all precautions not to inject directly into a vein, and also avoiding the injection of any air. He had about completed dressing when he said that he had a pricking sensation in the neck and chest; soon he sat down and said that he could not breathe, nor did he breathe again. I placed him upon the floor and called for help, and did all that seemed possible for him, but to no avail. His pulse at the wrist remained regular and full for some time after respiration ceased. He had a mild degree of cyanosis of the face, and the face was oedematous. He died in tonic spasm in ten minutes after receiving the serum." An inquiry was held and an autopsy made, but nothing was found to account for death.

Dr. Gillette subsequently collected and published the notes of 29 other cases of a similar nature, making 30 cases altogether; 16 of the 30 were fatal.[8] Most of them occurred in the United States. One such case has occurred in this country in the person of a young woman who died at Kidlington, near Oxford, in November, 1908, immediately after receiving a prophylactic dose of antitoxin.[9] I have not seen any account of this case in a medical paper.

The symptoms in this class of cases are usually intense dyspnoea, with failure of respiration and collapse. Very occasionally there is a rash, which is usually urticaria. You will have noticed that in the case of the immediate reaction in a little girl, which I related earlier, there were cyanosis and collapse. In cases of that sort there may be dyspnoea, though it is rarely so severe as it is in the cases of an immediate reaction after a primary injection. One very important fact remains to be mentioned with regard to the second class of cases, namely, that the sufferers have many of them been the victims of asthma or some allied disorder. In some cases they have been persons who have had a peculiar idiosyncrasy to horses. Dr. de Besche, for example, could not go near a horse or into a stable without getting an attack similar to the one he underwent after the injection of serum, but with much milder symptoms. Of the 30 cases published by Dr. Gillette 22 were the subjects of asthma or attacks of a similar nature. What the exact pathology of the attack is I do not profess to know. In the experiments on animals to which I have alluded above, the guinea-pig which has been sensitized to horse serum dies with symptoms which strongly resemble those of an attack of asthma in the human subject. There are respiratory embarrassment, coughing and sneezing, and breathing ceases before the heart stops beating. Auer and Lewis[10] claim to have shown that the symptoms in these animals are due to constriction of the bronchioles and carbonic acid poisoning. But some recent experiments of Manwaring[11] on dogs indicate that in those animals, at any rate, another cause is at work, some autointoxication of hepatic and intestinal origin. The symptoms that are observed in the human being suggest that in one set of cases there is interference with the mechanism of respiration, but whether it is at the centre or periphery is not clear. In another set of cases, and more especially those in which the reaction follows a reinjection, the symptoms lead one to suspect that there may be an affection of the respiratory mucous membranes like the urticaria which comes out at the same time all over the skin. Further observations, clinical as well as experimental, are required to clear these points up.

Antitoxin as a Prophylactic.

Now, what is the practical outcome of these cases and experiments? I think I have brought forward enough evidence to justify the modification I have made during the past few years in my views on the subject of serum administration. I have no desire to pose as an alarmist, but with a knowledge of such cases as I have narrated above I am quite averse from using antitoxin as a prophylactic. Not only might it happen that the person treated was especially and peculiarly susceptible to the action of serum, even if he was not known to be asthmatic, but supposing that he was not naturally susceptible, it would not be unlikely that by the injection you would render him artificially so, in which case, if subsequently it were found to be necessary to use antitoxin remedially—a by no means unlikely event in these days of serums and vaccines—he would run the risk of undergoing a very unpleasant illness. There are some instances of outbreaks of diphtheria in institutions for the care of children, in which the use of antitoxin as a prophylactic, given cautiously and after due inquiry into the children's life-history, may be justified. But I am strongly of the opinion that an indiscriminate use of serum as a prophylactic is not only unnecessary but unjustifiable.

The next question is, whether it is advisable to give antitoxin to persons who are only suspected to be suffering from diphtheria. The answer to this is that it is partly a matter of probabilities, and partly one of the age of the patient. As a rule, doubtful cases of diphtheria are not severe cases, and in the cases of individuals over 10 years of age a delay of a day or two will clear the case up and not prejudice the patient's chance of recovery. In patients under 10 there is only one class of cases in which the diagnosis is doubtful and the disease dangerous—namely, the laryngeal cases. Diphtheria not infrequently commences in the larynx, and, in the absence of exudation upon the fauces, it is very difficult to say whether the case is one of diphtheria or not. If you can exclude such well known causes of laryngeal obstruction in children as measles, retropharyngeal abscess, and the like, and are hesitating between a laryngitis due to diphtheria and one due to a less malignant organism, you must fear the worst disease, and bring against it the best remedy—namely, antitoxic serum.

Antitoxin in Undoubted Diphtheria.

In cases of undoubted diphtheria there is seldom necessity for hesitation as to the use of antitoxin. I should stay my hand only in the case of an asthmatic individual. If you are called upon to treat an asthmatic who has been unfortunate enough to contract diphtheria, you will have to choose between two evils. If the attack of diphtheria is severe, and especially if the larynx is involved, you will be compelled to risk his supersensitiveness. For, happily, it is not every asthmatic who is supersensitive. Dr. Gillette himself used to be one of those persons in whom an attack of asthma was set up by the presence of a horse. But he received two injections of horse serum which were followed only by very slight reactions, and apparently cured him of his peculiar susceptibility.

At the beginning of this paper I mentioned the importance of the early administration of serum in diphtheria. This is to be emphasized, not only because of its beneficial effect upon the course of the disease, but because the earlier the treatment is begun the smaller is the dose of serum that it is necessary to give. Smallness of dose, strictly speaking, implies fewness of units; but in practice it nearly always also means smallness of volume. It is undesirable to give large volumes, because the larger the volume the greater the chance of the occurrence of a serum reaction, and, in my experience, of the production of the anaphylactic state. Serum of low antitoxic potency is not so expensive as that of the high which it is necessary to employ in severe—that is to say, advanced—cases. Hence early treatment is the most economical. I am not accus-

tomed, however, to pay much attention to the history of the case, but to judge each on its merits, as I see it, though it may be taken as a rule to which there are few exceptions, that in severe cases the severity of the disease directly depends upon its duration. Severity of attack is shown by extent of exudation and symptoms of toxaemia.

The dose I am accustomed to give is from 2,000 units for a mild case up to 20,000 for a severe case, repeating half this amount the next day if there is any increase in the severity of the disease. In most instances this will be sufficient, but in very severe cases, especially of the haemorrhagic form, large doses should be injected. In one sense you cannot give too much serum; you cannot poison a person by an overdose, as you can with such drugs as morphine and strychnine. Nor is it necessary to take into consideration the age of the patient, unless it be to reverse the ordinary principles of dosage by giving larger amounts of antitoxin to children than to adults.

I have always administered serum by subcutaneous injection. No doubt the most efficacious method is by intravenous injection; but it presents considerable practical difficulties, of which the chief is that it is by no means easy to pick out a vein in a small child who is the subject of diphtherial toxaemia. Of administration by the mouth or rectum, advocated by some writers, I have no experience. I am certain that by hypodermic injection the serum will be retained and absorbed, but I am not so sure that it will be, in any given case, if administered by the channels mentioned.

Lastly, I will just touch on one question that may be asked, namely, can the unpleasant reactions I have been talking about be in any way prevented? So far as I know, they cannot; there is conflict of evidence on the subject. But neither heating the serum nor the use of any drug appears to be entirely efficacious, though there is clinical evidence to show that large doses of calcium lactate will mitigate the rash of serum sickness. Anaphylaxis can be produced in animals by feeding them on certain proteins, so that the rectal or oral administration cannot be expected to be free from risk of the unpleasant sequels. But this I will say, that it would seem as if there were some methods in the manufacture of the serum that were better than others so far as the avoidance of unpleasant effects is concerned; for certainly during the past few years the antitoxic serum supplied to the Asylums Board's hospitals has been less noxious than it was at one time. I have not, however, been able to ascertain the cause of the undoubted improvement that has been effected.

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A PRELIMINARY report by Captain Stevenson, I.M.S. (*The Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India;* new series, No. 38, 1910), on the killing of rats and rat fleas by hydrocyanic gas has been issued recently. Fumigation with this gas has been largely used by the agricultural departments in the United States of America and in South Africa, chiefly for the destruction of scale insects infesting plants. To produce the gas, an enamel ware vessel or a kerosene tin is placed in the middle of the room to be fumigated. Measured quantities of water and sulphuric acid are then placed in this, and when all is ready the potassium cyanide is dropped in, the operator bolting from the room as fast as he can get out. The man who measures out the potassium cyanide must use rubber gloves, otherwise he will almost certainly be poisoned, and the individual who drops it into the water and acid should do so at arm's length, retiring, as has already been said, as fast as he can. So deadly is the gas, that a whiff of fairly strong vapour kills at once. Further, as it is somewhat inflammable, no naked lights must be left about the buildings to be fumigated. Apparently the gas is harmless to the plague bacilli themselves, but is very toxic to fleas and their hosts the rats. The risk attending the employment of such a deadly gas as this would seem to be too great, at least for general use.

THE ARGYLL ROBERTSON SIGN IN CEREBRAL AND SPINAL SYPHILIS.

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THE frequency and importance of the Argyll Robertson sign in tabes dorsalis and general paralysis is a matter of general knowledge, but there still seems some doubt as to its incidence in cerebro-spinal syphilis. In Dr. Risien Russell's[1] very interesting opening address to the discussion on ophthalmoplegia at the Annual Meeting of the British Medical Association last year, he asked the pertinent questions as to how far persons who have had syphilis and have the Argyll Robertson sign have escaped tabes or general paralysis, and whether this sign is compatible with a syphilitic lesion which does not mean a tendency to progressive degeneration. It was disappointing that in the discussion which followed no decisive answers were given to these questions, desirable as it is that a point of such diagnostic importance should be settled.

Dr. Mott,[2] in a discussion on syphilis in the Neurological Section of the Royal Society of Medicine, said on this point: "There is one sign usually present which for all practical purposes is only met with in parasyphilis—namely, the Argyll Robertson pupil. No coarse random lesion will explain the constancy of this phenomenon; moreover, this condition, although a sign of syphilitic infection, does not occur in true syphilitic brain disease."

The Argyll Robertson phenomenon is to be regarded as an example of the selective action of a poison upon the central nervous system, inasmuch as a special group of neurones having a definite and restricted function is picked out and put out of action. It may be compared in this respect with the action of the diphtheritic poison in paralysing accommodation. The parasyphilitic affections offer other examples of similar selective action of the virus—for example, the disease of certain fibres of the posterior roots in tabes. In cerebro-spinal syphilis, however, such results are conspicuously absent, the paralyses there met with are produced as the consequence of interference with the nutrition of the neurones by occlusion of vessels from endoarteritis or thrombosis, by their compression by exudation, or by destruction through gummatous tumours. *A priori*, therefore, it would be unlikely that a sign like the Argyll Robertson pupil should occur in cerebro-spinal syphilis.

In 1903, in a paper[3] on this subject based on the analysis of 37 cases of syphilis of the brain and cord, I concluded that previous syphilis is not sufficient without some further change to lead to the presence of this sign; that its presence is evidence of a degenerative process at work within the nervous system, and this process is to be regarded as a "parasyphilitic" one; but that it is reasonable to suppose that the degenerative process, of which the Argyll Robertson sign is one of the symptoms, may remain stationary at an early stage, or for a long period without further development. An example of this arrest is seen in some cases of tabes dorsalis. With some exceptions to be mentioned later, this view, if correct, would practically confine the sign to parasyphilitic infections.

In a recent analysis of 48 cases of syphilis of the brain and 21 of the cord, 69 in all, I obtained the following results with regard to the Argyll Robertson pupil. In every case there was a clear history of syphilis, or some undoubted syphilitic lesion, and, in addition, in the later cases Fleming's test was positive. Out of the 69 cases, the Argyll Robertson pupil was present in 2 of cerebral syphilis. One of these was a man of 32, apparently with syphilitic meningitis of the convexity; he had headaches, was apathetic, forgetful, depressed, with indistinct or slightly slurring speech and exaggerated knee-jerks. He showed no improvement under treatment, and his symptoms suggested the possibility of an early stage of general paralysis. The other patient was a woman, aged 45, who suffered from right facial paralysis twelve years ago, five years ago was under my care for cerebral syphilis, with right hemiplegia and