TETANUS:

ITS PREVENTION AND TREATMENT BY MEANS
OF ANTITETANIC SERUM.

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TETANUS cannot be said to be of frequent occurrence under ordinary conditions of life in time of peace, but the outbreak of war is often followed by a comparatively large increase in the number of cases of this disease.

These notes, the fruit of work in a serum laboratory and of a slight cultivation of the literature, were gathered together some months ago without any idea of their appearing in their present form, and I now publish them with the object of calling the attention of those who have not specially studied the question to the value of tetanus antitoxin, which is inestimable when the serum is used properly as a prophylactic. It is to be hoped that at the present time systematic use will be made of this remedy, so that one, at any rate, of the hazards run by those who are offering their all on the battlefield in defence of their country may be reduced to a minimum.

HISTORICAL.

Tetanus, or lockjaw, is a malady common to man and many animals. It was recognized in ancient times, and it has long been known that it was likely to follow the soiling of wounds with earth, dust, and similar material. About the middle of the nineteenth century the impression gained ground that it was due to the production of a poison in the wound, and in 1834 Carle and Rattone reported that they had conveyed the disease by means of pus from a case of tetanus.

In 1835 Nicolaier produced tetanus in mice, guinea-pigs, and rabbits by inoculating them with garden soil, and the pus from the wounds carried on the infection from animal to animal. In the local lesion Nicolaier found a bacillus with a spore at the end, but he did not succeed in obtaining a pure culture.

In 1836 Rosenbach found a similar bacillus in a case of human tetanus, but he also was unsuccessful in his attempts to isolate it. Knut Faber (1839) separated the toxin from mixed cultures by means of filtration through porcelain. Kitasato in 1889 was the first who succeeded in securing a pure culture of this bacillus and in proving that it alone was the causal agent of the disease.

DISTRIBUTION OF THE BACILLUS.

The *Bacillus tetani* is widely distributed in nature, being found in the soil of most cultivated areas, in the streets of cities, and in fact in any place where there is faecal contamination. v. Lingelsheim recalls the examination by Bossano of samples of dust from thirty-eight towns, only twelve of which were found free from tetanus bacilli. Nicolaier found it in twelve out of eighteen samples of earth in the neighbourhood of Göttingen.

Choukévitch (1911) demonstrated its presence in the intestinal contents of two horses out of eighteen, but Lukas (1914) was more successful, as he isolated it from the faeces of sixteen out of seventeen horses. Joseph (1910) examined the excreta of cattle, and came to the conclusion that the *Bacillus tetani* must be considered a normal inhabitant of the intestine of these animals. Römer (1909) also found it frequently in the faeces of adult cattle, but it was not usually present in animals under 2 years of age. Further, tetanus antitoxin was found in the blood of the older animals in more than 50 per cent. of the cases examined. Dolly (1910) found tetanus bacilli frequently in the wads of blank cartridges, and Graser (1910) reports a like result. Rabinowitsch (1907) found the spores of this bacillus in the water in which strawberries sold in Berlin had been washed. It is said to have been found in the mud of the Dead Sea.

This wide distribution of the organism emphasizes the necessity for extreme care in cleansing all wounds, but especially those which have come in contact with street dust, road sweepings, the soil of cultivated fields, garden earth, manure, etc.

Bahnson (cited by Anders and Morgan) stated that during the American Civil War he was put with other prisoners into a shelter that had been used for horses, and that all the wounded placed there who did not die as a direct result of their wounds developed tetanus, and all of them died.

CULTIVATION OF THE BACILLUS.

Under the usual conditions of artificial cultivation in pure culture, the tetanus bacillus will not grow in the presence of oxygen, and therefore it is termed an "anaerobic" organism. But if some nutrient medium be inoculated with the *Bacillus tetani*, and also with some oxygen-loving organism such as the *Bacillus subtilis* (hay bacillus), the absence of oxygen is not so necessary, as the *B. subtilis* will use up the oxygen and produce conditions in which the *B. tetani* can grow. Further, Tarozzi and others have shown that if pieces of animal tissue be placed in a liquid culture medium the bacillus will grow alone in the presence of oxygen, the dead tissue acting as a reducing agent.

In nature we get a combination of these two methods of producing conditions suitable for growth; in the earth we have organic materials to act as reducing agents and the aerobic organisms to use up oxygen; in contused and dirtied wounds we have the dead tissues and the pyogenic cocci to act in a similar manner.

PRODUCTION OF TETANUS TOXIN.

Tetanus toxin is prepared by growing the tetanus bacillus in nutrient bouillon, of neutral or slightly alkaline reaction, which may or may not contain some reducing agent such as glucose, sodium sulphindigotate, etc. Special flasks filled with such a broth are inoculated with the tetanus bacillus, hydrogen gas is passed through the liquid and the flasks are placed at 37° C. for eight to ten days, when the bouillon is filtered through porcelain to remove the bacilli and spores. The filtrate forms the tetanus toxin. The toxicity of such a filtrate varies very much. A mouse of 15 grams weight might be killed in three to four days by 50 $\frac{1}{100}$ c.cm., or it might be necessary to inject 1 $\frac{1}{100}$ c.cm. or even more. The susceptibility of different species of animals to this toxin varies very markedly; thus it is stated that if a certain quantity of toxin will just kill 1 gram of mouse the same quantity will kill—

6 grams of guinea-pig	1/600 gram of cat
12 " of horse	1/1000 " of goose
1/2 gram of goat	1/4000 " of pigeon
1/150 " of rabbit	1/30000 " of hen

from which it is evident that the horse is one of the most susceptible of animals.

PRODUCTION OF TETANUS ANTITOXIN.

In 1890 Behring and Kitasato showed that animals could be immunized against the tetanus bacillus and its toxin, and that then their blood had acquired a new property, so that when it was injected in suitable quantity into other animals these were protected against doses of tetanus which otherwise would be invariably fatal. This new property, they thought, was due to the development in the blood of immunized animals of a substance which, as it neutralized the toxin, they called "antitoxin." When the fluid part of the blood has been separated from the solids it is found that the antitoxin is contained in the plasma or serum. Horses are the animals most frequently used in the production of tetanus antitoxin for therapeutic purposes. As they are so highly susceptible to the toxin the utmost care is required during the process of immunization to avoid the occurrence of accidents. Therefore, at the beginning of the immunization the toxin is not given in the pure state, but only after having been modified by chemicals or by being mixed with antitoxin. Sometimes the toxin and the antitoxin are not mixed, but are given simultaneously in separate parts of the body or the antitoxin is given a few hours before the toxin. Whichever method is used at the commencement, the object is always the same, namely, to produce a basal immunity so that after a time the animal will bear without ill effect the inoculation of pure toxin. Therefore, as the injections are repeated the amount of modifying agent is gradually decreased until only toxin is given. When the establishment of a basal immunity has been demonstrated the

loses are increased more rapidly, and finally 200 c.cm., 400 c.cm., or 1,000 c.cm. of pure toxin are injected at one time. The inoculations are usually given subcutaneously or intramuscularly (though some use the intravenous route) at intervals of five to ten days. After the final dose a rest of one to three weeks is given before the animal is bled, when on an average 8 litres of blood are withdrawn. If considered desirable another bleeding may be taken at the end of a week, and followed by a third, fourth, or fifth at intervals of seven or eight days. The animal then has a rest of three weeks or more before being reimmunized. During a bleeding, as well as during all subsequent processes, every precaution is taken to prevent contamination. When the plasma or serum has been obtained separate from the corpuscles and clot, a small amount of preservative is added, and it is put away in a cool dark place for a time.

As soon as possible after a bleeding the serum is tested to ascertain whether it contains enough antitoxin to render it fit for therapeutic use. This standardization is carried out according to the American method introduced by Rosenau and Anderson (1908), a description of which has been published in *Bulletin* No. 43 of the United States Public Health and Marine Hospital Service and in the *Journal of Hygiene*, January, 1914.*

When required for use the serum is filtered through porcelain and distributed into small bottles. Before being sent out for therapeutic use antitetanic serum is tested—

1. *For absence of toxicity* by animal experiment, 10 c.cm. of serum being injected subcutaneously into each of two guinea-pigs of 250 grams weight. The animals must remain well.
2. *For sterility* by cultural experiment aerobically and anaerobically. The media inoculated with the serum must not show any growth.
3. *For non-excess of preservative*, 0.5 c.cm. of serum being injected subcutaneously into a mouse of 15 grams weight. The animal must not show more than temporary symptoms of intoxication.

From the time the serum is first obtained its antitoxin content begins to diminish. This diminution takes place most rapidly at first; later the serum appears to reach a condition of comparatively stable equilibrium, when the deterioration proceeds much more slowly. To compensate for this unavoidable loss there is usually put into each bottle an amount of antitoxin in excess of the quantity stated to be present, sufficient to make it probable that the bottle will, at the end of two years, contain the amount of antitoxin stated on the label, provided it is stored in a dark cool place—preferably in an ice-chest.

PROPHYLACTIC USE OF TETANUS ANTITOXIN.

Tetanus antitoxin may be used (1) prophylactically, (2) curatively.

As a prophylactic tetanus antitoxin yields excellent results.

Animal experiment has proved:

That if a fatal dose of tetanus toxin be mixed together with a suitable amount of tetanus antitoxin, the mixture can be injected into animals without giving rise to any ill effect whatever.

That the effect of a fatal dose of toxin can be completely inhibited by the injection of antitoxin twenty-four hours previously.

That a fatal result can be prevented by injecting a suitable dose of serum within a short time of the injection of the toxin.

From these results it would naturally be expected that tetanus antitoxin would furnish good results when used as a prophylactic. Such has been the case.

Vaillard (1912, p. 224) refers to the practice of eight veterinary surgeons from 1898 to 1906. In that period they inoculated 13,124 animals after operations or accidental wounds, and not a single case of tetanus occurred among them. During the same time two veterinary surgeons alone saw 139 cases of tetanus among animals which did not receive the treatment. If the figures of Nocard and Labat are added, we get 16,917 animals which had a prophylactic injection, and among them one single horse had tetanus—in this case the antitoxin was given five days after the wound, and the attack was very benign.

* The Lister Institute serum is thus standardized.

Huguier (1909) used to give two injections of 10 c.cm. each of antitetanic serum, but for some years has been content to give one, and, although he operated in conditions under which infection was most possible, he has not had one case of tetanus among horses thus treated prophylactically.

Dieudonné (1909) records 1,009 operations for castration or hernia, with no case of tetanus, although only a single injection of serum was given. During the same period he observed 87 cases of tetanus among horses operated on or wounded which had not had a prophylactic injection.

Parker Hitchens (1910) has proved experimentally that a dose of 300 U.S.A. units of tetanus antitoxin will protect a horse against an infection fatal to the control animals.

Mohler and Eichhorn (1911) found experimentally that as regards an infection fatal to the control—

300 U.S.A. units given 48 hours after infection =	no symptoms of tetanus.
500 U.S.A. units given 72 hours after infection =	no symptoms of tetanus.
700 U.S.A. units given 96 hours after infection =	no symptoms of tetanus.

Whereas—

250 U.S.A. units given 48 hours after infection =	local tetanus. Recovery.
400 U.S.A. units given 96 hours after infection =	local tetanus. Recovery.

They conclude "that 500 U.S.A. units is a sufficient dose of antitoxin for use as a prophylactic, even in cases where the infection has occurred four days prior to the injection of antitoxin."

The experience of veterinary surgeons is therefore all in favour of the value of the prophylactic use of antitetanic serum. The results of its use for a similar purpose in the human subject are scarcely less decisive.

Vaillard (1912) cites the experience of Biron and Pied. These surgeons did not use serum from 1895 to 1902, and had during those years 11 cases of tetanus, which were all fatal. In 1903 they began to use serum systematically in every case in which there was a chance of infection with tetanus. From 1903 to 1910 there was not a single case of tetanus in their practice, but during this period they received into their wards 4 cases of tetanus from outside; 3 cases of tetanus were taken into other wards of the same hospital, and there were 2 deaths from tetanus in the town. Vaillard refers also to cases of tetanus following wounds received during the celebrations on July 4th (Independence Day) in America. In 1903 there were 415 cases of tetanus. Then the prophylactic treatment was strongly urged and began to be made use of.

In 1904 there were	...	...	105 cases.
In 1905 " "	...	...	104 "
In 1906 " "	...	...	89 "
In 1907 " "	...	...	73 "

These figures suggest that, as the years passed and the beneficial results were recognized, more and more attention was devoted to prophylactic serum treatment.

Confirmatory evidence has also been brought forward by Brandenstein (1908); Bockenheimer (1909); Solieri (1910), thirty-five cases with one death; Graser (1910), no case of tetanus in eight years among patients treated prophylactically; Simon (1913, p. 236), citing Liell's analysis of 350 cases of July 4th wounds and tetanus, shows a mortality of 98 per cent.; only seven recovered and of these five had prophylactic treatment. In 1907 the editor of the *Journal of the American Medical Association* summed up the case as follows:

A fairly careful scrutiny of the American literature for the past five years has not brought to light a single report of the development of tetanus in a person who received a timely prophylactic dose of tetanus antitoxin.

We thus see that the inestimable value of tetanus antitoxin when properly used as a prophylactic is beyond question.

In connexion with the words "properly used" in the previous sentence it is important to remember that antitetanic serum is an antitoxic and not a bactericidal serum. It has no power to inhibit the growth of the bacillus. All antitoxin can do is to neutralize the toxin produced. A certain amount (x) of serum can neutralize a certain amount (y) of toxin and no more. Any further

toxin produced can exercise its deleterious effect uninfluenced by the serum. Thus if an animal has been infected by tetanus and has received a prophylactic dose of serum it is protected against the toxin produced until the neutralizing power of the serum has been exhausted. When that stage is reached, then, as Vaillard puts it, if more toxin is elaborated one of three things must happen, either:

1. More antitoxin must be given; or
2. The animal must produce its own antitoxin; or
3. The animal must become intoxicated.

Further (cf. Tarozzi *supra*), the tetanus bacillus can multiply and produce toxin in blood clots, or in necrotic tissue, especially in the depths of a wound; and as there is some evidence suggesting that a sharp fall may occur in the antitoxin content of the blood about one week after an injection of antitoxin, it is advisable to repeat the injections weekly as long as there is any necrotic tissue in a wound. Again, there may be necrotic tissue in a wound several days old, or a large amount of dirt may be ground into the tissue—for example, run-over cases—and it may be decided to operate and thoroughly clean up such a wound. In this case it is advisable to give a prophylactic dose of antitoxin intramuscularly some hours before the operation, as acute tetanus has occurred within twenty-four hours of such operation, and has in all probability been due to the rapid absorption, by the fresh tissues laid bare by the operation, of a large dose of tetanus toxin which had been elaborated in the necrotic tissue, or was present in the dirt with which the wound was soiled.

Dose.

The amount of serum which should be given at each injection depends entirely upon the number of units in each cubic centimetre of the serum. We have seen above that for the horse, which is the animal most susceptible to tetanus poison, the Americans have experimentally demonstrated the dose to be 300 to 500 U.S.A. units; but in the case of man we have no such evidence. v. Behring recommends 10 to 20 units. These units are German units, and one of them is equal to about 40 U.S.A. units. The dose would then be 400 to 800 U.S.A. units.

Vaillard mentions 10 c.cm. as the dose for superficial easily-cleaned wounds, not grossly soiled; 10 c.cm. of the tetanus antitoxin sold by the Pasteur Institute usually contains from 500 to 1,000 U.S.A. units.

Tizzoni considers that 200,000 of his own units is an ordinary prophylactic dose. I have only examined one sample of Tizzoni's serum.¹ The bottle contained 5 c.cm. = 200,000 units Tizzoni = 125 units U.S.A.

Park and Williams (p. 243) say: "It is the custom at many dispensaries in New York City and elsewhere to immunize all Fourth of July wounds by injecting 1,000 units. None of these have ever developed tetanus."

From this last statement we would conclude that 1,000 U.S.A. units is an ample prophylactic dose, as it has always prevented tetanus, and that it is quite possible a smaller dose would answer the purpose. This apparently has been found to be the case by von Behring, Vaillard, and Tizzoni.

Where there is plenty of serum at the disposal of the surgeon there is no need to take thought about the size of the dose, and the ample dose of 1,000 to 1,500 units may be given with the knowledge that it is better to give too much than too little. But when, as may easily happen during war, there is only a limited amount of serum available, then the question of the smallest protective dose becomes important. This may be put down as about 500 U.S.A. units for a simple uncomplicated case, and as the amount of soiling of the wound and contusion of the tissues increases so should the amount of antitoxin be increased.

The interval of time between the infliction of the injury and the injection of serum also has to be taken into consideration when fixing the dose. Dönitz (1897) showed experimentally in rabbits that if an hour were allowed to elapse between the injection of the toxin and that of the serum it required forty times the neutralizing dose (*in vitro*) of serum to save the life of the animal. Studying the same question recently on guinea-pigs I found that while $\frac{1}{10}$ U.S.A. unit of antitoxin neutralized 100 minimal

lethal doses (M.L.D.) of tetanus toxin *in vitro* it required 1 unit of antitoxin to neutralize 1 M.L.D. when given subcutaneously and simultaneously but in different parts of the body, but 3 units did not save life when given four hours after the toxin. When the serum was given twenty-four hours after 1 M.L.D. of toxin it required 2,000 units of antitoxin to save life, though even this amount did not prevent the onset of the disease. In these animals 1 M.L.D. almost always caused the appearance of slight signs of tetanus at the end of twenty-four hours after the injection of toxin.

It is obvious, then, that the earlier the prophylactic dose is given the more certain will be its effect in preventing tetanus, the smaller within limits will be the dose, and the smaller the cost of treatment. This last item may seem insignificant, and it is so when it is only a question of the prophylactic use of antitoxin; but it will be found to loom large in the picture when it is necessary to consider the value of tetanus antitoxin from a curative point of view.

CURATIVE USE.

"*Premonitory*" Symptoms.—In all diseases the earlier the treatment is commenced the greater the chances of a favourable result. If we could recognize tetanus in a stage as early as we can diphtheria, it would no doubt be possible to obtain just as good results from serum treatment. But tetanus, unlike diphtheria, has no characteristic lesion which appears early in the attack and gives an indication of the nature of the disease. As it has been aptly put by Dr. C. J. Martin, the diagnostic membrane in diphtheria corresponds to the dirt or other foreign body carrying the infection of tetanus, and so, just as we give diphtheria antitoxin when we see such a membrane, so ought we to give tetanus antitoxin when we see any such infecting material in a wound. When the symptoms of tetanus are distinct it means usually that the disease has made very considerable headway, and has reached that stage which in diphtheria would be looked upon by some as beyond the reach of the beneficial influence of antitoxin.

This explains to some extent the uncertain results which follow the use of antitoxin as a curative agent, and it also raises the question whether there are any "premonitory" symptoms the presence of which might rouse a suspicion that a case was one of commencing tetanus. A study of some of the literature of tetanus has shown that commencing tetanus has been mistaken for "colds," muscular rheumatism, stiff neck, sore throat, influenza, mumps, etc., and it has even been suggested that many cases which have been diagnosed and treated successfully as cases of the above diseases have in reality been slight attacks of tetanus. With the object of directing attention to what may prove to be "premonitory symptoms," K. Evler (1910) relates 13 cases of tetanus with 2 deaths, which came under his personal observation, he himself being one of them. He describes these "premonitory" symptoms as being very varied and changeable.

A day or so after the infection there may be general restlessness, changing suddenly to a desire to rest.

Sleeplessness with distressing dreams, and it may be nightly delirium.

Difficulty in micturition due to spasm of the sphincter vesicae, which may last from a few minutes to half an hour.

Temporary giddiness, violent headache, excessive yawning.

The facial appearance changes and the patient looks anxious, though there is no risus sardonicus yet.

There may be trembling of the tongue which is put out to one side.

There is often a profuse sweating, and darting pains in various parts may occur.

The patient may have a feeling of chilliness, and there may be some swelling, without redness locally, of the injured member and throbbing of its arteries notwithstanding that the limb is raised.

Slight jerking may follow pressure on the flexor tendons, and these muscles may be noticed to be in a condition of increased irritability.[†]

[†] This condition of increased irritability of the flexor muscles has been noticed to occur in horses quite early in an attack of tetanus.

* Cf. *Journal of Hygiene*, January, 1914.

If symptoms such as these are present with a history of possible infection with the tetanus bacillus Evler considers that the administration of serum is justified. The later symptoms include:

- Increased flow of saliva.
- Reflex cramps of oesophagus.
- Ocular symptoms; for example, nystagmus, strabismus.
- Ear trouble, and spasmodic cough.
- Tremors and clonic spasms which are not painful and which may not attract attention.
- Pain persisting after muscular contraction induced by effort.
- Swollen and reddened lymphatics, enlarged glands and tenderness in the infected region.

Evler infected himself during an operation and early symptoms developed within twenty-four hours. He presented nearly all of the symptoms mentioned. Serotherapy was commenced on the fifth day. Nutrient enemata became necessary on the seventeenth and eighteenth days, but on the nineteenth the teeth could be opened a little and recovery then progressed satisfactorily.

Evler's paper directed my attention to these "premonitory" symptoms, and since reading it I have carefully read through a considerable number of cases of tetanus described in the literature, and I have found that practically all the symptoms mentioned by Evler have been noticed as being present early in the disease. All have not been observed in the same patient, but usually the one or two present have been sufficiently prominent to force themselves upon the notice of the physician, and, if he had read Evler's paper, to remind him that such a disease as tetanus might be before him.

If tetanus be studied from the standpoint of these "premonitory" symptoms, there is reason to hope that as our knowledge of them increases so will our power of combating the disease be increased by our intervention earlier in an attack.

Curative Value.

The results following the use of antitoxin as a curative agent have been up to the present for the most part unsatisfactory. The reasons given to account for this are that the disease is usually diagnosed only when it has made considerable progress, and that the toxin is absorbed and travels along paths where it is beyond the influence of antitoxin.

In most cases the tetanus bacilli remain and multiply at the site of infection, and the toxin there produced is absorbed and carried to the central nervous system. As regards the path by which it travels, numerous observers have corroborated the findings of Meyer and Ransom that tetanus toxin is chiefly absorbed from the infected wound along the motor nerves of that region, and passes by direct extension into and through the spinal cord, but it may also pass into the circulation. It is also thought that in the nerves the toxin passes along the axis cylinder. Some observers, however, do not agree entirely with these conclusions.

Cernovodeanu and Henri (1907) have stated that if the vessels and muscles of a limb be tied while the nerves remain intact, a large amount of tetanus toxin may be injected without the production of tetanus, and they therefore conclude that, while some toxin is absorbed by the nerves, the larger part passes along the lymphatics and blood vessels.

Field (cited by Park and Williams) is of opinion that the toxin does not pass along the axis cylinder but along the lymphatics of the nerves.

Permin (1912-1913), from a critical analysis of the literature and from the results of a large number of experiments performed by himself, concludes that part of the toxin is taken up by the peripheral muscle nerves of the site of infection and passes along the axis cylinder to the spinal cord, and part passes into the lymph and blood and gaining the general circulation may pass directly to the ganglion cells of the cord or indirectly by means of the peripheral nerves.

There is, then, no unanimity of opinion as to the special road taken by the toxin, but what we know is that somehow the toxin passes along the nerves comparatively rapidly, but the amount found in the cerebro-spinal fluid is not great—on several occasions 1 to 2 c.cm. of this fluid have contained a fatal dose for a mouse but not more toxin than this.

The holding of the opinion that the toxin is absorbed by the nerve endings and passes along the axis cylinder—that is, in a situation which is beyond the reach of antitoxin in the blood—renders the curative treatment of declared tetanus practically hopeless, in the opinion of many clinicians. Antitoxin does not appear to penetrate readily into the substance of the peripheral nerves or of the central nervous system, and therefore all it can do is to neutralize only the toxin which has not been absorbed, or which is in the blood stream. (After huge doses of antitoxin, given intravenously, only traces of it can be found in the cerebro-spinal fluid.) So a cure can result from the employment of antitoxin only so long as a fatal dose of toxin has not been absorbed. Many cases are on record, and many experiments which seem to confirm this view.* The experiments of McClintock and Hutchings (1913) will serve to illustrate this point. They took sheep with long tails and inserted into the tip of the tail a splinter of wood which had been infected with tetanus spores free from toxin. The first symptoms of tetanus occurred six to eight days later, when the tail was at once amputated, 20 cm. being removed, and 4,500 U.S.A. units of tetanus antitoxin were given intravenously and repeated daily. Every animal but one died and the symptoms did not seem to be influenced by the serum. The amount of toxin in the blood, as proved by animal experiment, was at its maximum between the fifth and seventh day—2 c.cm. of blood containing a fatal dose for a guinea-pig of 350 grams weight. No toxin was found in 2 c.cm. of the blood twenty-four hours after the injection of serum.

From these results it has been concluded that as amputation of the tail had no effect upon the progress of the disease, and as there was toxin in 2 c.cm. of the blood before but not twenty-four hours after the commencement of serum treatment, therefore by the time that the first signs of tetanus appeared a fatal dose of toxin either had been absorbed and fixed, or if not completely fixed was in a situation where the antitoxin could not reach it to prevent complete fixation. This being the case, all that can be expected from serum treatment is the prevention of further absorption of toxin by blocking all the paths leading from the infected area—the nerve routes by injection into the nerves of the region affected and the vascular route by large injections into a vein—and all this merely in the hope that a fatal dose of toxin has not already been absorbed.

It is not certain, however, that these views are correct. They may be based on a false premiss, namely, that antitoxin must penetrate into the cell before it can neutralize the toxin attached to the cell.

But the recent work of Kraus and Amiradzibi (1910) suggests that, contrary to the usual acceptance, a toxin must pass out of a poisoned cell before it can be neutralized by its antitoxin, as the latter cannot penetrate into the cell; and further, that the rate of diffusion of the toxin out of the cell is accelerated by the presence of antitoxin in the surrounding fluid.

Moreover, von Graff and Menschikoff (1912) have shown experimentally that it is possible to extract tetanus toxin from liver cells by means of antitoxin. They allowed the cells to remain in contact with a solution of toxin during one hour at 37° C. Then they removed the cells and washed them free from surrounding toxin. Some of these washed cells were injected into mice and caused tetanus. The remainder were soaked in a solution of tetanus antitoxin for one hour at 37° C., and then removed from the serum, washed free from surrounding antitoxin and injected into mice, which remained quite well. Control experiments showed that while toxin could pass into the cell and be so firmly fixed that several washings would not remove it, serum, on the other hand, could not pass into the cell in any demonstrable quantity. It is justifiable, therefore, to presume that the toxin was extracted from the cells by the surrounding antitoxin, and that it is advisable to have as high a concentration of antitoxin as possible in the fluids surrounding poisoned cells.

This view of the action of the antitoxin gives more encouragement to the physician to persevere vigorously with serum treatment. It emphasizes the advisability of employing very large doses of serum so as to saturate

* Note.—For a most excellent review of the literature of this subject, cf. Permin, 1913.

the system with antitoxin, and thus not only neutralize any toxin which may be passing from the focus of infection into the blood, but also to extract toxin from cells into which it has already passed.

Such treatment, suggested by the results of experimental research, is practically identical with that employed by many physicians to-day as the outcome of years of bedside observation.

Ernest E. Irons (1912) analysed the 252 cases collected by Anders and Morgan* and classified them. The incubation periods of the fatal and non-fatal cases showed practically the same relation. His figures are:

Total number of cases	252	Mortality.
Cases treated without serum	142	71%
Cases treated with serum	112	63%
Cases treated with small amounts of serum	71	70.4%
Cases treated with large amounts (100 c.cm. or more) of serum	41	51.0%

If we compare the mortality of all the cases treated with serum with that of the cases treated without we must allow that the use of serum brings little if any advantage. But if we compare the mortality in cases treated with large amounts of serum with the mortality of the cases treated without serum, then the beneficial results following such use of serum become manifest.

W. H. Park (1910) says that when a large intravenous dose is given within a few hours of the onset of the symptoms the effect is marked. More than 50 per cent. of the patients so treated recovered, "some of whom I feel perfectly sure would have died without the serum." At the first sign of actual tetanus 10,000 to 20,000 U.S.A. units should be given intravenously, and followed every twelve hours by further injections. The later injections may be given subcutaneously if the intravenous route becomes difficult. Torres (1912), after an experience of 110 cases of acute tetanus in eight years with a mortality of 32.7 per cent., gives an intravenous injection of 120 c.cm. of serum as the rule. He repeats it twice, or even oftener, in the first twenty-four hours if necessary, and then gives 100 c.cm. daily if the symptoms are still present.

Penna (1913) also gives injections of 100 c.cm. intravenously once or twice in the twenty-four hours, and keeps it up for several days *even though the patient may be improving*.

Van der Bogert (1913) cites:

1. Strock (1907) who treated his cases of tetanus during six years with small doses of serum and had a mortality of 100 per cent. Then he treated 5 cases with very large doses and the mortality was 20 per cent.

2. The 3 cases of Young (1912) which appeared hopeless, but recovered—a boy had 150,000 U.S.A. units, a man had 220,000 U.S.A. units, and a girl of 14 years had 587,000 U.S.A. units.

Many other similar records could be quoted, if space permitted, to show that among those who not infrequently meet with cases of tetanus the tendency of late years has been to use much larger doses of antitoxin than formerly, and that the use of these large doses seems to be followed by more uniformly beneficial results than were observed in former years when only small doses were employed.

Modes of Administration.

Besides the size of the dose the mode of administration of the serum has an influence upon the result. Serum may be given—

1. Intracerebrally.
2. Subarachnoidally.
3. Intraneurally.
4. Intravenously.
5. Intramuscularly.
6. Subcutaneously.

1. Intracerebral injections have given very good results in animals and in several cases in man also, but the risk of permanent injury to the nervous system has prevented this method coming into general use. Ballance (1914), however, suggests that the introduction of serum into the lateral ventricle might be used in tetanus, as he thinks that with reasonable care the operation as a whole is free from danger.

3. Intraneural injections were strongly recommended by Rogers (1905), but they are not free from risk, and are seldom used.

4, 5, and 6. As regards the intravenous, intramuscular, and subcutaneous route the final result is the same in all three. The only difference is in the time taken for the antitoxin to be absorbed and distributed throughout the body. In the case of the intravenous method it is a question of a few minutes; of the intramuscular, of a few hours; while after subcutaneous injections it is one to two days before the maximum concentration of antitoxin in the blood is reached. There remains the subarachnoidal route to consider.

Descos and Barthélemy (1902) experimentally showed that intraspinal injections gave the best result.

Von Graff (1912) carried out a number of experiments in the Serotherapeutic Institute in Vienna, and came to the conclusion that this route was the most effective, and that next to it came the intravenous.

Permin (loc. cit.) considers that intraspinal are just as good as intraneural, and are better than intravenous, inoculations.

W. H. Park (1914, personal communication) has treated 6 successive cases of tetanus by intraspinal injections, and all have recovered.

Hofman (1907) states that of 13 cases which had serum beneath the skin, 53.8 per cent. died, whereas of 16 cases which had serum subdurally only 12.5 per cent. died, and these 16 cases included a number of extremely severe cases with brief incubation periods. He recommends that the intraspinal injections should be given every two to three days and the subcutaneous daily. Graser (1910) also advises serum by intralumbar injection every two to three days and daily beneath the skin. Gobiet (1904), Neugebauer (1905), Jeric (1908), and Buffagni (1910) and others speak of the good effect of intraspinal injections of antitoxin, and Buffagni says:

1. After the first injection one observes an increase in the symptoms, reaching a maximum in forty-five hours, and then passing off and giving place to improvement.
2. The organization of the patient reacts to each injection of tetanus antitoxin by a rise in temperature of 1.5° to 2°C., which passes off in ten to twelve hours.
3. After each injection more or less distinct improvement of all conditions occurs, and especially of the tetanic attacks.†

The method of procedure in the serum treatment of a case of tetanus would then be somewhat as follows:

1. The injection beneath the arachnoid, or in very severe cases even (Ballance, 1914) into the lateral ventricle, of as large a dose of antitoxin as may be conveniently given—for example, 3,000 to 8,000 U.S.A. units.
2. The injection into a vein of a large dose—9,000 to 16,000 U.S.A. units—with the object of flooding the system with antitoxin as soon as possible.
3. The injection of antitoxin intramuscularly, and
4. The repeated injection of antitoxin subcutaneously—both with a view of keeping up the concentration in the blood.

Clinical experience both in man and horse has shown that it is absolutely necessary to continue the injections, even though improvement has apparently set in, as otherwise the symptoms are very liable to return—in some cases with greater intensity than at first.

"IDIOPATHIC" TETANUS.

The absence of any history of injury sometimes makes the diagnosis of tetanus at first very difficult. In the past such cases were classed as rheumatic or idiopathic tetanus, but we know now that for tetanus to declare itself the tetanus bacillus must somehow have gained entry into the body.

It has been shown experimentally that tetanus spores free from toxin or foreign material may be injected into animals without causing tetanus, and that they can become disseminated in the body and remain latent for a time. Then if suitable conditions arise, such as the formation of a necrotic area in the tissues, such latent spores may germinate and give rise to tetanus.

Cantora (1907) infected animals subcutaneously with tetanus bacilli and found that they spread all over the body. He also injected toxin-free tetanus spores and found them in the blood twelve hours later. They may remain in the blood for ten to fifteen days, during

† These observations of Buffagni are very like those made by some physicians with regard to intraspinal injections of antimeningo-ocic serum.

which time very slight injuries are sufficient to set up tetanus. Later, the spores became localized in the liver, spleen, lungs, kidneys, lymph glands, and marrow, where they may remain latent for some months.

Semple (1911) came to the conclusion that an injection of a solution of quinine might cause enough destruction of tissue to produce conditions favourable for the germination of spores.

It behoves us, therefore, to bear tetanus in mind, even though there be no history of injury, whenever we meet with symptoms similar to the premonitory symptoms mentioned by Evler and found to be present in so many cases of this disease.

PRESERVATIVES IN SERUM.

Most serums have a small amount of preservative (phenol, trikresol, chloroform) added to them, and when doses such as 120 c.cm. are given at one time the presence of preservatives requires consideration and raises the question as to how much preservative can be given without ill effect.

Baccelli (1911), who strongly recommends that tetanus should be treated with subcutaneous injections of carbolic acid, states that not less than 1 gram should be given daily; J. H. Haberland (1913) in a case of hydrophobia gave 22½ grains of phenol subcutaneously in twelve hours without any evidence, either locally or generally, of any deleterious effects; Natali (1899) injected 5.25 grams of phenol subcutaneously in eighteen days; and Ascoli (1898) gave 75 c.cm. of a 3 per cent. solution without any subsequent toxic symptoms.

The probability of ill effects being due to the preservatives in serum when administered intrathecally has been fully discussed and negatived by Flexner in the case of automeningococcal serum. It may, then, be safely assumed that the amount of phenol put into serum is not likely to have any serious consequences.

CONCLUSIONS.

Tetanus may be cured by the administration of antitoxin, provided that the serum treatment is begun early in the attack and is pursued vigorously and continuously. Unfortunately in the present state of our knowledge a diagnosis is as a rule made only when the disease is in a stage so advanced as to make the results of treatment uncertain, even though very large doses of antitoxin are used. These large doses are costly, and place the serum treatment of tetanus practically out of the reach of those with shallow purses—unless, of course, the serum be provided by the State. But in the prophylactic use of serum there is within the reach of every one a means of checking the disease. It has been proved beyond the shadow of a doubt that, wherever the prophylactic use of antitoxin has been carried out systematically, tetanus may be said to have disappeared. Tetanus should therefore be looked upon as a preventable disease, and, when one realizes this, there flashes across the mind the memorable question, "If preventable, why not prevented?"

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INSECTS AND WAR:

IV.—THE FLOUR MOTH IN SOLDIERS' BISCUITS.

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Where moth . . . doth corrupt.—MATT. vi, 19.

It is not only insects which destroy the continuity of the soldiers' integument which play a part in war. It has been well said that an army marches on its stomach, and the admirable commissariat arrangements which have been so distinct a feature of the British Expeditionary Force during the present war are the result of much patient care and attention during times of peace. Every one knows that recruits are frequently rejected for some defect in their teeth. A soldier, indeed, requires strong teeth, for his farinaceous food in the field is largely supplied to him in the form of biscuits—not that "moist and jovial sort of viand," as Charles Dickens described the Captain biscuit, but hard tack which challenges the stoutest molars.

During the summer of 1913 the authorities of the British Museum at South Kensington arranged a very interesting but somewhat gruesome exhibit in the Central Hall. The exhibit consisted mainly of army biscuits covered by horrible webs or unwholesome looking skeins of silky

Fig. 1.—*Ephestia kuehniella*. Moth-infested biscuit.

threads, eaten through and through by the larva of a small moth. Together with these were certain long metallic coils and other apparatus used in investigating certain phases of the life-history of the moth and the manufacture of the biscuit. The exhibit illustrates an article¹ which had recently appeared on the baking of army biscuits, by