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Paper concerning the latest developments in the treatment, immunization, and prophylaxis of tetanus : including a report on 389 prophylactic injections given at Fort Crook Bomber Plant

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A Paper Concerning The Latest Developments In The Treatment, Immunization, And Prophylaxis Of Tetanus: Including A Report On 389 Prophylactic Injections Given At Fort Crook Bomber Plant

By
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I N T R O D U C T I O N

Within the following pages the author has endeavored to intelligently cover all of the headings included in the rather imposing title found on the previous page. The body of this paper includes a comprehensive review of the literature of the past five years concerning prevention, treatment, and immunization of tetanus.

At the end of this thesis there is a report on 389 prophylactic injections of tetanus anti-toxin that were given to men who were constructing the Fort Crook Bomber Plant during the spring and summer of 1941. I wish to express my sincere appreciation to Dr. R. W. Fouts of Omaha who granted me free use of his files; also I wish to thank Dr. Joseph Weinberg, Dr. J. W. Duncan, Dr. W. L. Sucha, Dr. J. E. Courtney and Dr. W. E. Holmes, for their invaluable contributions to my report on the prophylactic injections. Because, among the various reactions encountered from the injections of tetanus anti-toxin there were several neuritic complications, the report at the end of this paper includes a review of nerve complications resulting from prophylactic injections of tetanus anti-toxin.

It is my sincere intention not to make this paper a series of quotes; it is my intention to write a logical composite picture of the treatment, prevention and immunization of tetanus. May my results be as good as my intentions.

I N D E X

PART I

GENERAL CONSIDERATIONS

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As will be shown in this paper, the majority of authorities agree that tetanus antitoxin is the chief factor in treating cases of tetanus, and that immunization of all children with the alum precipitated toxoid can reduce the appalling mortality rate of 40-60%. Also, most men who have had contact with a good many cases of tetanus agree that excellent nursing care and adequate sedation are just as important as the antitoxin.

It is often a very difficult job to know what type of wound merits prophylactic treatment, formerly it was supposed that only deep puncture wounds resulted in tetanus, but the past decade has proven this to be a fallacy, for tetanus infection may result from the slightest laceration. In fact there are certain types of wounds where the physician rarely, if ever, gives tetanus antitoxin for prophylaxis, for example injuries to the eye seldon result in tetanus, D. G. Cogan (1) reports that there are only 29 cases in the world lit rature, and that 14 of these cases have occurred since the use of antitoxin. Cogan also brings out that the majority of these injuries were due to objects associated with horses, such as whips, or objects that had been in contact with the ground, such as horseshoes and pitchfoks. This report of Cogan's is certainly not contradictory, for tetanus spores have been proven to be just about anywhere; particularly are the spores likely to be in fertilized earth. Cogan goes on to mention that

these 29 cases were all associated with severe suppurative infections not caused by the Clostridium tetani, and that all of these cases were fatal. Of course one cannot conclude from these 29 cases that a suppurative infection imposed on a case of tetanus causes a more severe tetanic reaction, but I have found in reviewing the literature that a case of tetanus complicated by a suppurative infection was more inclined to be fatal than a case of tetanus wherein there was no infection. I have brought Cogan's report in here at this time to illustrate that tetanus can occur in most any type of wound; therefore there is a great responsibility placed on the physician, for he must determine if it is necessary to give tetanus antitoxin, or to give a "booster" dose of toxoid, if the patient has been previously immunized. The clinician should thoroughly analyze each wound; naturally if it is a puncture type, the wound readily heals over on top and provides excellent anaerobic conditions for the tetanus bacillus. Also the instrument that caused the wound should be taken into consideration; if the instrument was the prong of a pitchfork that had been imbedded in a pile of manure, then there would be little hesitation about taking the usual prophylactic measures. However, as stated before, tetanus may result from any type of wound; consequently it is impossible to cite any definite criteria as to when prophylaxis for tetanus should be given. It seems to me that the physicians' own conscience is the best criteria; if

you can't sleep nights because you failed to take the necessary precaution then by all means give the patient the antitoxin. I do not mean to infer that the antitoxin should be given out to every patient with an injury, for as will be brought out later some very serious complications may arise from giving tetanus antitoxin to the wrong person. It is of interest to note at this point that the state of Indiana holds the attending physician responsible if one of his patients develops tetanus and the prophylactic injection had not been given. Indiana even provides a fund to buy antitoxin for those who cannot afford the expense. (2).

Dietrich and Karshner (3) in a report covering 28 cases of tetanus showed that 70 percent of these cases suffered compression fractures in one or more vertebrae near the apex of the dorsal curve. All of these fractures occurred in children, and these two men explained the fractures as the result of the tetanic convulsions hammering the bodies of the vertebrae together. There are no symptoms from this type of fracture; however, the area involved may show a flattening, which, as the author points out, is rather contradictory, as one would expect a kyphosis. Also these two men state that any sort of treatment of these fractures is of no avail; the damage done to the vertebrae of these children cannot be repaired. Consequently, one may infer from this article that adequate sedation in a child suffering from tetanus may save the child from a severe back injury.

As I have intimated before it is not wise to give any type of horse sera blindly; adequate precaution should always be taken. Forman (4) in an article in the Ohio State Medical Journal emphasizes that a complete history of any allergy on either side of the family must be obtained, which would include asthma, vaso-motor rhinitis, migraine, and hay fever; also any idiosyncrasies, such as hives, from certain foods, weeds, or flowers. Particularly should there be inquiries made as to whether the patient gets any reaction when he is around horses, or if he has had horse sera before. Forman insists that it should be a rule that horse serum should never be given until a skin test has been done, he even goes so far as to say that not only should you skin test with horse serum but also with horse dander. If there is any doubt as to whether the skin test is positive or not, then a conjunctival test should be done. Patients who have been found to be positive to horse serum or dander can be de-sensitized by injecting 1 to 2 cc's of serum or dander as an initial dose then increasing the dose by 1 cc every half hour until the required amount is given. In persons who prove to be positive to both horse dander and serum, it is best to change to another type of serum. Now to most physicians who see a great many traumatic wounds this time-consuming and rather bothersome method of skin testing and de-sensitization may seem to be a waste of time, but I believe that if you have ever had experience with some of the more severe complications that

horse serum can produce you would gladly go through all of the tests not once but twice.

It was formerly the supposition, and some physicians still harbor the erroneous belief, that anaphylactic shock may be avoided if the tetanus antitoxin is given while the patient is in deep anaesthesia, but in 1937 Quill (5) reported a case of anaphylaxis in a young man who had received tetanus antitoxin while he was in ether narcosis. This case prompted this same author to run a series of experiments on dogs, rabbits and guinea pigs; a group of each of these animals were sensitized to horse serum, then the animals were put in deep anaesthesia with ether and then given "shocking" doses of horse serum. Every single animal showed signs of anaphylactic shock. Also this same technique was carried out on non-sensitized animals and there were no signs of anaphylaxis in any of them. Therefore, Quill arrived at the conclusion that ether narcosis does not prevent anaphylactic shock in any way. In 1939 Koontz and Shackelford (6) carried out a similar experiment to Quill's on guinea pigs alone and they found that ether narcosis decreases anaphylaxis in guinea pigs, but the authors of this article maintain that their work cannot be applied to man, because the guinea pig is extremely sensitive to horse serum, hence whatever protection the ethernarcosis would give would be very marked in guinea pigs. The dogs used by Quill are about as sensitive as man to horse serum, and Quill showed that anaphylaxis is not prevented by ether narcosis in dogs. I believe that it may be con-

cluded from these experiments that ether narcosis may have some effect in cutting down anaphylaxis in sensitized guinea pigs, but it has no affect on rabbits or dogs; therefore it is not safe to assume that ether narcosis will prevent anaphylaxis in man.

PART II

ANIMAL EXPERIMENTS IN TETANUS

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In reviewing the literature on tetanus I found that a great deal of experimental work has been done in regards to the efficiency, dose, point of injection, and proper time to give tetanus antitoxin. Therefore I feel that a special section should be dedicated to this experimental work:

In 1938 Abel and Chalian (7) carried out a series of experiments on dogs and monkeys in order to determine the most favorable time for administering tetanus antitoxin, and if it was possible to neutralize toxin that had been previously fixed by tissues. The technique involved giving the animals a certain number of minimal lethal doses of tetanus toxin; then after a period of time the toxin that was left in the blood was washed out; by determining the amount of toxin in the blood it was then simple to calculate how much of the toxin was fixed in a given length of time. All of these dogs were saved from death by the administration of antitoxin; therefore Abel and Chalian concluded that it was possible to neutralize fixed toxin. In a later series of experiments carried out on dogs and monkeys these same two men found that toxin in the blood stream is readily neutralized by tetanus antitoxin. This latter part of the experiment was carried out by merely not washing out the toxin first but given the antitoxin after the toxin had been injected into the blood stream, then examining the blood for free toxin. By following this experimental technique, as roughly out-

lined above, it was concluded that serum therapy is of no avail in cases of descending tetanus where one or more minimal lethal doses have been fixed by the tissues before the antitoxin is given; that in tetanic animals whose tissues have fixed many lethal doses of toxin, those animals can be kept from showing signs of tetanus if the serum is given before a certain period of time has elapsed in the incubation period. In cases where one to three minimal lethal doses have been given you cannot wait longer than forty hours before giving serum if you wish to avoid signs of tetanus, if ten or more minimal lethal doses are given you cannot wait longer than twenty-four hours before giving serum if you wish to avoid signs of tetanus. It is impossible to save life if there is evidence of descending tetanus and one or more lethal doses of toxin have been fixed. However cases of tetanus may be saved if there is descending tetanus, but less than one lethal dose of tetanus has been fixed in the tissues. Abel and Chalian also conclude from their experiments that cases of local tetanus can readily be saved by giving adequate and continuous amounts of antitoxin, for in local tetanus the local tissues fixed as much toxin as is possible then the remainder of the toxin is thrown into the blood stream and eventually becomes fixed in other tissues thereby fixing much more toxin and so increasing the severity of the infection. Finally, Abel and Chalian concluded that the amount of toxin fixed by the tissues is decisive for life or death, that any toxin that is "left over" in the blood stream is useless.

It is quite evident from examining the various reports in the literature that there is quite a controversy as to the safety and rationale of injecting tetanus antitoxin into the spinal canal.

In 1939 Schumacker, Lamont and Firor (8) showed that dogs, cats and monkeys could be killed with roughly the same amount of toxin per kilogram of body weight if it was given into the motor end area of the spinal cord. The three species of animals were used because the monkey is sensitive to toxin (tetanus), the dog is resistant to tetanus toxin, and the cat is even more resistant to tetanus toxin than the dog. Two hundred dogs, forty cats, and fifteen monkeys were all injected with so many lethal doses of tetanus toxin per kilogram in the motor end area of the spinal cord, and all of the animals showed the following signs in order: back leg reflexes became hyperactive, vague movements of hind legs, clonic movements of hing legs, then an inability to stand. These animals did not die as they received their injections into the lower lumbar area, hence this portion of the experiment shows that the toxin was fixed in the cord at point of injection. Other animals of the three species named were injected in other parts of the cord and it was found that they all had the same signs of tetanus when they were given the same amounts of toxin per kilogram. As a consequence of these experiments it was rationalized that the various degrees of immunity in the various species of animals depends upon their ability to neutralize tetanus toxin be-

fore it became fixed in the spinal cord.

In 1940 Schumacker, Lamont and Firor (9) carried their experiments in species differences in resistance to tetanus toxin a bit further, and injected guinea pigs, mice, dogs and cats (the guinea pig being the most sensitive to toxin and the cat the least sensitive to toxin) with tetanus antitoxin intra-venously, and at the same time injected these same animals with tetanus toxin in various sites, then they determined how much of the toxin had been neutralized. These men found that the greater the sensitivety of the animal to the toxin the less the amount of toxin that was neutralized, and that if the toxin was given in the spinal cord it took seven thousand times the amount of antitoxin to neutralize the toxin, if the toxin had been given intra-venously as well as the antitoxin; also it took four to twenty times more antitoxin if the toxin was given intra-muscularly or sub-cutaneously; the antitoxin was most effective when the toxin was also given intra-venously; however still better affects were obtained when the toxin and antitoxin were mixed together in vitro, then the mixture given intra-venously. Schumacker, Firor and Lamont (9) make no attempt to explain why animals that are the most sensitive to tetanus neutralize less amounts of toxin then the more resistant animals. They do however explain that it would naturally take more antitoxin given intra-venously if the toxin is given directly into the tissues, then if the toxin is given into the bood stream, for the toxin in the tissues is very readily fixed, hence difficult to neutralize, and the toxin is even more difficult to neutralize when it is injected into tissues it has a special affinity for, such as the spinal cord.

In view of the above findings Schumacker, Firor and Lamont (10) attempted to treat cases of tetanus in dogs with antitoxin by giving the antitoxin by various routes, and these men reported that the intra-thecal method of giving antitoxin was the most successful way of treating moderately severe tetanus. They stressed that the tetanus should be only moderately severe, for the best results with intra-thecal administration, for these investigators implied that if the tetanus was only mild then the dogs got well even if the antitoxin was given sub-cutaneously or intra-venously, and if the tetanus was too severe then no method of giving antitoxin was satisfactory. These men also reported that dogs with severe tetanus who were treated with intra-thecal antitoxin lived longer than those dogs who had severe tetanus and were treated by the intra-venous or sub-cutaneous route. The report on the latter series of experiments is concluded with the idea that the exact intra-thecal doseage is not known, nor is it known whether the cisternal or lumbar routes are best. In an article written by Firor (11) he discusses the experiments just previously mentioned, and Firor intimates that one should not conclude from these experiments that the intra-thecal route is the best route in man, for he notices that in the dogs there often resulted a sort of bulbar poliomyelitis when the serum was given intra-thecally; particularly was this true in dogs with severe tetanus. Firor suggests that this bulbar reaction may be eliminated if it was possible to obtain a human serum from those who had been previously immunized with tetanus toxoid; or by a finer purification process of the

serum with proteolytic enzymes. Firor closes his article with the statement that the experiments he and his associates carried out (Schumacker and Lamont) (8-9-10) are not conclusive as to the importance of whatever meningeal damage may result from the intra-thecal administration of tetanus antitoxin; he also states that there is no difference in efficiency of antitoxin if it is given in lumbar region or cisternal region.

Yodh (12), Vener and Bower (13), who will be mentioned again in the clinical reports of treatment of tetanus, all highly recommend that patients with tetanus should be given serum by the intra-thecal route. This idea is contrary to Firor's report that one should at least hesitate before giving a human antitoxin intra-thecally. Also Dietrich (14), who will be mentioned in a later chapter, strongly advises that the intra-thecal route should not be used, and that great caution should be used in giving antitoxin by the intra-venous route because of the severe bulbar reactions that may result, and because of inflamatory changes in the meninges. Dietrich (14) severely criticizes Yodh (12), who had reported low mortality rates when using the intra-thecal route, for not including in his mortality percentages those that died within twenty-four hours after they came under his (Yodh's) care. Yodh rationalized that those who died within the first twenty-four hours would have died no matter what was done, so he subtracted those twenty-four hour deaths from his mortality and obtained what he called a net-mortality. Dietrich claims that perhaps those early deaths were

caused by the intra-thecal administration of antitoxin.

This so-called bulbar poliomyelitis that Dietrich (14) and others attribute to the intra-thecal and intra-venous use of tetanus antitoxin is, according to Dietrich, not a tetanic thing but more or less resembles a poliomyelitis that has involved the bulbar region. Dietrich also claims that this bulbar reaction is not an allergic manifestation, otherwise epinephrin should control the bulbar seizures. In my search for some explanation for this bulbar reaction I encountered a theory proposed by W. E. B. Hall (15). However, Hall supposes that the reactions are of a tetanic nature, or "acute massive tetanismus." This theory is titled, the Phenomena of Toxin Release, which, in brief, is as follows: Tetanus toxin in combined form is released from the easily dissociable combination as a result of post-prophylactic loss of antitoxin; there is then a subsequent development of a anti (antitoxin) or anti-amboceptor, and there is then the final violent combination of the heavy theropeutic antitoxin and the anti (antitoxin) or anti-amboceptor with the subsequent release of free toxin. In other words, Hall believes that before the "massive tetanismus" can occur the patient must have been sensitive to the anti-toxin then this sensitivety is lost and a anti (anti-toxin) develops, then if tetanus develops and huge therapeutic doses of antitoxin are given the anti (antitoxin) unites with the therapeutic antitoxin and free toxin is liberated. This is especially true if the therapeutic antitoxin is given in a tissue that has a

particular affinity for tetanus toxin. The theory may be likened to the replacement of a weak acid by a strong acid in a unstable acid-base combination i.e., toxin-anti (antitoxin) plus antitoxin equals antitoxin anti(antitoxin) plus free toxin. The impetus for this theory was the fact that Hall had three cases of acute massive tetanismus after intra-thecal administration of tetanus antitoxin, and each of these patients were sensitive to the antitoxin before it was given intra-thecally, but all three of the patients had been de-sensitized before the therapeutic antitoxin was given; however the sensitivety had been present long enough for the anti (antitoxin) to develop. Hall points out that even in persons with negative skin tests it is dangerous to give the antitoxin into a tissue that has an affinity for the toxin, for it is entirely possible that a person may have once been sensitive, then lost that sensitivety and the anti (antitoxin) may have developed. The part of the toxin that is released in the cases of so-called "acute tetanismus" is the tetanospasmin. By the same theory as given above tetano hemolysin may be released when therapeutic antitoxin is given directly into the blood stream, Hall reports three cases of hemolysis (1 death) in persons who had previously received intra-venous serum before.

I have presented Hall's therory not because I believe it explains the bulbar poliomyelitis mentioned by Dietrich (14), for these bulbar reactions have occurred in persons who have never

had a previous injection of tetanus antitoxin; therefore in those cases it would be impossible for the anti (antitoxin) to develop; unless of course a person could naturally acquire this anti (antitoxin), which is not probable, but because I believe it is worthy of consideration, for perhaps the bulbar poliomyelitis and the acute tetanismus are two separate entities.

The theory that tetanus toxin follows the nerves has long ago been discarded, for it is now generally accepted that the toxin is transmitted by the blood stream, but just how the toxin combines with the blood was a question until about two years ago when Shwartzman (16) injected guinea pigs with twenty to forty minimum lethal doses of tetanus toxin, then bled these guinea pigs from the heart. The blood was pooled, defibrinated with glass beads, filtered, contrifuged. Some of the cells were washed four times with sodium chloride, these cells failed to produce tetanus when injected into a guinea pig, but the unwashed cells did produce tetanus when injected into a guinea pig. It was found that the amount of toxin present in the blood was in direct proportion to the amount of hemoglobin present; so it was concluded that the toxin attached itself to the hemoglobin probably the oxy-hemoglobin.

While I have just previously stated that at the present time most everyone is convinced that tetanus toxin follows the blood stream; it was not so very long ago that everyone was also convinced that the toxin followed the nerves of the organism. However, Speath (19) states that if the toxin did follow the nerve

path ways then the disease should vary with the location of the lesion, and in his series he found that this was not true; also if the "herve theory" were true there should be more clossical pictures in tetanus, of first involving ~~apholic~~ cephalic nerves and then proceeding to the nerves of the extremities. Speath also reminds us that the belief that toxin follows nerve path ways was so long prevalent because it was difficult to prove that the blood was toxic; he accounts for this difficulty in the following:

(1) Blood may have been taken from an animal who was very sensitive to toxin; therefore all of the toxin may have been fixed in the tissues.

(2) It is necessary to inject large quantities of toxic serum before any effect can take place.

(3) Recipient animals of the toxic blood may have been resistant to the toxin.

(4) Amount of actual toxin present may have been very low.

(5) Tetanus upsets the metabolism to such a degree that all of the toxin may have disappeared. Whenever all of these factors are taken into consideration it is quite a simple matter to prove that the blood of a tetanic animal is quite toxic.

As will be seen later one of the first treatments for tetanus was the use of phenol (Babes 1898) and the phenol treatment has been revived on and off ever since that time. In May, 1941, Thompson and Friedman (17) conducted experiments on dogs that definitely proved that phenol was of no value in treatment of tetanus. First the length of time was determined it took a dog to die when given

one hundred dog-lethal doses (100 D.L.D., kills in 25-46 hours). Next three dogs were given 100 D.L.D., and six hours later a 1:4000 solution of phenol was given intra thecally; three other dogs were also given 100 D.L.D., plus a two hundred times the neutralizing dose of tetanus antitoxin was given intra-thecally, in one dog the therapy was combined, and several other dogs were just given phenol alone. From this experiment the results obtained were: the dog that received the phenol for treatment of tetanus died sooner than those dogs who received no treatment for their tetanus, dogs that received the two hundred times neutralizing dose of antitoxin were saved (it was further determined that the dogs could be saved with a dose of 182 times neutralizing does, if it were given within a six hour period). On post-mortem examination of the dogs who received the phenol intra-thecally, a toxic myelopathy of central nervous system was noted with thickened meninges, there was also noted a simple nephrosis of kidney with passive congestion, and the liver showed passive congestion with degeneration; these later conditions were noted on post-mortem examination when the experiment was carried further and an attempt was made to save dogs who were given one hundred D.L.D., and at the same time given 1:4000 solution of phenol, both given intra-venously; however here again the phenol only caused the dogs to die sooner than if they had not received the phenol. So from these experiments it was concluded that the tetanus antitoxin is very definitely superior to the phenol, in fact the latter is more toxic than

the tetanus itself. Consequently, I believe that the post-mortem examinations of those dogs who received the intra-thecal phenol are sufficient reasons why tetanus antitoxin should probably not be given intra-thecally, for quite often phenol is used as a preservative in the antitoxin, and even if the phenol is present in small amounts it can cause irritation to the meninges.

It would indeed be very convenient if it were possible to give tetanus victims a standard dose of antitoxin and know that they were adequately protected. Speath (19) attempted to prove in June 1941 that a single intra-muscular or intra-venous dose of 20,000 to 100,000 units of antitoxin was sufficient to ward off a lethal dose from 6-42 days. Speath took blood from twenty-six persons who had been actively treated for tetanus by receiving 20,000-100,000 units of antitoxin. White mice and guinea pigs were given various amounts of tetanus toxin, then the blood serum from the treated patients were given to the animals. The time for death of animals was noted, and the amount of toxin neutralized was determined by titration. These titrations indicated that the length of time a high titer is present in the blood is not directly proportional to the amount of antitoxin given. Speath's clincial experience with a standard dose will be mentioned later.

In summation; the animal experiments previously described resulted in the following conclusions:

Abel and Chalian

1. It is possible to neutralize fixed toxin if

sufficient quantities of antitoxin are given.

2. Antitoxin must be given before a lethal dose of the toxin becomes fixed in tissues.

Schmaucker, Lamont and Firor (8-9-10-11)

1. Spinal cord tissue has a special affinity for tetanus toxin.
2. No matter what the sensitivety of the animal to tetanus toxin, the same amount of toxin per kilogram injected into the cord kills all species.
3. Intra-thecal administration of antitoxin is an excellent avenue for injection of antitoxin in moderately severe cases of tetanus in dogs.
4. A reaction similar to a bulbar poliomyelitis may result when antitoxin is given intra-thecally.
5. It takes many hundred times more the usual neutralizing dose of antitoxin to neutralize tissue fixed toxin, then if the toxin were free in the blood stream.
6. The greater the sensitivety of an animal to tetanus toxin the less the amount of toxin that is neutralized by the antitoxin.

Hall (15)

1. An acute tetanismus or ~~neolysis~~ HEMOLYSIS may be explained by the Toxin Release Theory.

Thompson and Friedman (17)

1. Phenol has little or no effect in the treatment of tetanus and may cause serious damage to the tissues.

Schwartzman (16)

1. Toxin in the blood stream is in combination with oxy hemoglobin.

Speath (19)

1. A sufficiently high protective liter of antitoxin is obtained in the blood stream for a period of 6-42 days by one intra-venous or intra-muscular injection of 20-100,000 units of tetanus antitoxin.

While animal experimentation is invaluable to the progress of medical science, I firmly believe that the results of clinical experience proves the true value of any medical procedure. Hence I shall now attempt to compare the various clinical methods in the treatment of tetanus.

PART III

CLINICAL TREATMENT OF TETANUS

It was mentioned earlier in this paper that phenol was one of the first therapeutic agents used in tetanus (Babes 1898) (Baccelli 1911). In 1931, before Thompson and Friedman (17) conducted their experiments on the efficiency of phenol, Suvansa (18) revived the phenol treatment, using a 1:400 solution of phenol in thirty to forty cubic centimeters of saline, and injecting the mixture intra-thecally. Suvansa claimed that in the fourteen cases treated only four of the patients died;however, in a later series of twelve cases treated with phenol five of the patientsdied. At the present time Suvansa uses tetanus antitoxin, but he still maintains that phenol is very good in mild cases of tetanus. Personally I believe that phenol may be excellent for a mild case of tetanus, but a mild case of tetanus is rather difficult to diagnose, for often what appears to be mild suddenly blossoms out as a severe case of tetanus, and I do not believe that an intelligent clinician would take the risk and just give phenol alone in even a so-called mild tetanus.

Tetanus antitoxin can literally work a miracle if given in early stages to a tetanus victim; consequently it is very important for the clinician to recognize the earliest onset of tetanus. Jensen (20) emphasizes such early symptoms as sore throat, pain across back and difficulty in swallowing as indicative of early tetanus; particularly when there is a history of some sort of wound. This author also recommends that immediate ~~iodical~~ surgical ex-

icision of the wound should be done, expecially if the wound is infected with facultative staphylococcus or streptococcus of the hemolytic variety, for these organisms make an excellent necrotic nidus for the tetanus bacillus. Rarely do the tetanus spores leave the site of innoculation; in several rare instances the spores have been found in the spinal fluid, therefore if a complete excision of the wound is done the source of the toxin is eliminated. Jensen also points out that if gas gangrene develops, the gas infection will cause the tetanus to lie dormant; consequently gas infected victims should receive tetanus prophylaxis.

While Jensen (20) believes the surgical debridmont of the wound is a great aid in helping the tetanus patient, he also insists that an adequate amount of antitoxin be given, but Klopp (21) insists "that an ounce of clean surgery is worth several pounds of serum therapy." In using the surgical approach as the only direct method of saving a tetanus patient Dr. Klopp is overlooking that some of the toxin may be already fixed in the tissues, and all the clean surgery in the world will not save the patient if sufficient amount of the toxin is fixed; however it may be quite likely that the antitoxin cannot neutralize fixed toxin, but that is getting ahead of the story.

While expermiental evidence points to the fact that intrathecal and intra-venous therapy may prove disastrous to the patient, Canwarden (22) reports three cases of tetanus that were cured completely with intra-venous and intra-thecal administration of anti-

toxin. One case received 16,000 units intra-venously and 4,000 units intra-thecally; two other cases received 180,000 units intra-venously followed in twenty-four hours by 40,000 units intra-venously. Naturally these three cases are not sufficient to prove that the intra-venous and intra-thecal methods are entirely safe.

Cables (23) reports the cure of a single case of tetanus with the usual trismus, risus sardonicus, opisthotonos, ~~and~~ stiff neck and ~~the~~ rigid abdomen. The patient was also subject to severe convulsive seizures, which were kept under control with 25 percent intra-muscular magnesium sulfate, and soluable pheno borbital, 2 grains sub-cutaneously every four hours. Besides the sedation the patient received a total of 3,450,000 units of antitoxin of which 700,000 units were given intra-venously, and 2,760,000 units were given intra-muscularly. It is of interest to note that Cables gave epinephrin (2 cc's) intra-venously along with each intra-venous injection of antitoxin. There is little doubt that the intra-venous epinephrin would ~~not~~ aid in preventing anaphylactic shock, but in the previous discussion of the so-called "bulbar polio" it was stated that epinephrin was of little use.

Yodh (12) who was previously mentioned in this paper, and severely condemned by Dietrich (14) for using the so-called net mortality rate, (subtracting all those patients who died within twenty-four hours after coming under his care) gives a review of 438 cases of tetanus treated with intra-venous, intra-muscular, and cisternal antitoxin. Yodh's total mortality was 50.6 percent

(net mortality 29.4 percent). The usual procedure in treating these cases was to give immediately 40,000 units of antitoxin cisternally, 40,000 units intra-venously, 40,000 units intra-muscularly; then every day thereafter give 40-80,000 units either intra-muscularly or intra-venously. Yodh claims in this article that the patients who received the antitoxin cisternally did much better than those patients who did not get any antitoxin cisternally. The author does not discuss the patients who died in the first twenty-four hours, in other words, he does not mention whether the deaths resembled a bulbar poliomyelitis. Yodh's contention that intra-thecal administration is a desirable avenue for the injection of antitoxin is in disagreement with Dietrich (14) and others who believe that this method of treatment is dangerous to the life of the patient. Dowler (24) reports one case of successfully treated tetanus in which 20,000 units of antitoxin were given intra-thecally, and a subsequent examination of the spinal fluid showed no abnormalities. However, this is the report of only one case; consequently it cannot be concluded that the intra-thecal avenue is entirely safe in all cases. Yodh (12) used paraldehyd (2 drachms in 2 ounces of saline per rectum) as a source of sedation, while Dowler in his one case used avertin. Most authorities agree that most any type of sedation is good; provided it is used in sufficient amounts, and that it does not depress the respiratory center, or "knock out" the cough reflexes, for so often patients die of an aspiration pneumonia by regurgitating stomach contents during a con-

vulsive seizure.

Firor (25) believes that the barbiturates and avertin both tend to depress the respiratory center; so he recommends the use of paraldehyde in oil per rectum or choral. Firor is also much against the intra-thecal use of antitoxin and the use of magnesium sulfate as a sedative, for he believes magnesium sulfate is too painful when given intra-muscularly and patients who are tetanic should not have such stimuli. Also Firor states that the sub-cutaneous use of oxygen (set up aerobic conditions about the wound) is of little use. The usual method of treatment ~~and~~ by the latter author is to give one initial dose of 50,000 units intra-muscularly, infiltrate around the wound with 10,000 units, then one hour after the former two procedures have been done to excise the wound thoroughly. Each following day 5,000 units are given until symptoms disappear. Seizures are controlled with the sedatives mentioned above. Normal fluid balance is maintained with a nasal tube if the patient has trouble swallowing; also an adequate diet is maintained, and if necessary an artificial respirator may be used or a tracheotomy may be done.

Apropos of the fact that Yodh has condemmened the use of avertin Maxison (26) reports eleven cases of tetanus treated with antitoxin (intra venous and intra muscular) and avertin. Four of the cases lived and seven died. I am not by any means inferring that the seven deaths were due to the avertin; for as Maxison points out the seven patients that died all succumbed within twenty-four

hours; therefore they probably did no receive enough avertin to cause death.

Mitchell (27) Cole (28) Beinheim (29 and Brebner-Smith (30) have all used avertin in one or more cases, and they all believe avertin to be an excellent narcotic for use in tetanus. The average rectal dose was about 100-125 mg. per kilogram given in three divided doses over a period of twenty-four hours. Cole (28) and Mitchell (27) both report that epinephrin and carbon dioxide inhalations both counter-act the respiratory depressent affect of avertin. The ~~use~~ case that Cole (28) reported was that of an infant who received a total of 80 basal doses of avertin, and the child suffered no affect; therefore Cole (28) concludes that avertin must be of a low toxicity.

Bryant and Fairman (31) and Earle (32) report on the successful use of evipan sodium. Earle (32) used 1 gram of the drug intra venously per twenty-four hours for the first three days of treatment; using chloretone (40 grains per rectum) if additional sedation was needed during the first three days.

Davis (33) in reporting on the use of pentathol sodium states that this drug is of little value for its action is far too rapid; however the drug may be of great benefit when it is necessary to transport the tetanus patient. Naturally this drug is used intra venously and if the puncture of the needle should set off a convulsive seizure there is great danger of perivenous injection which may lead to a very severe local reaction.

Farrell (34) reports the successful use, in one case, of nembutal, 63 grains orally, and 75 grains intra venously were given over a ten day period (individual doseage was 7.5 grains intra venously and 4.5 grains orally).

Peter Paterson of Glasgow, Scotland (36) is a strong advocate of the use of magnesium sulfate; his usual method was to give 2-2.5% solution in 40 cc' water sub cutaneously every four hours; by using the sub cutaneous route Patersonstated there was very little pain involved from the hypertonic solution. A colleague of Paterson's, Lyoll (35) reported the successful treatment of a tetanic patient when using 90 cc 's injection of a 3.5 percent solution of magnesium sulfate every four hours for the first two days, then using 40-50 cc of a 5 percent solution for a week. As time went on the dose was gradually reduced.

As seen from the last several reports a great variety of anaesthetics have been used, and each author seems to have his favorite, the favorite depending on the success he has had in using that aneasthetic. I do not believe that any one has the right to condemn or recommend a narcotic agent for use in tetanus unless the degree of tetanus is closely evaluated in each case. Obviously, in the mild cases of tetanus where little sedation is necessary the toxicity of a depressant is not so important, but in the severe tetanic cases where large continuous doses of a depressing drug are necessary the toxicity of the drug used must be taken into consideration. The

ideal drug to be used in tetanus is, of course, one that controls the convulsive seizures with a minimum amount, yet does not depress the respiratory center or "knock out" the gag reflex. Most of the depressants to be had today are not ideal; each depressant has some drawback. Paraldehyde is rapidly excreted by the respiratory system, but quite a bit must be given for anaesthesia, and often instead of depressing the patient this drug causes excitement. Avertin is a much more potent drug than paraldehyde; it is detoxified in the liver and excreted by the kidneys, therefore if the liver is not in good condition it is not wise to use this drug, for if it is not detoxified there may result kidney and liver damage similar to that caused by chloroform. Magnesium sulfate is painful to the patient, and there is too long a period for the full effect to be reached, and then the effect does not last long. The barbiturates depress the respiratory center. I believe that the best method for anaesthesia in cases of tetanus is the use of avertin per rectum augmented by small doses of one of the barbiturate derivatives, the latter may be given orally or rectally; the dose of each of these would vary according to the seriousness of the case. It is best to use avertin in a solution of amylene hydrate; otherwise there is severe initation of the rectal mucosa. Intra venous glucose is also recommended when using avertin in order to aid the liver in its detoxification of the drug. As I have had no actual experience with avertin, I possibly should not recommend it, but in reviewing the literature it was quite apparent that the majority of authors had used or recommended using avertin.

Freedlander (37) reports a series of 59 cases with a mortality of 53 percent from 1927-1939. The last 34 cases treated had the serum given intra thecally as well as intra venously, and the mortality from this group was 64.4 percent, the first group of 25 patients were treated only by the intra venous method, and the mortality here was only 27 percent. The author comments that three out of four patients who received the serum intra thecally died. Therefore, Freedlander believes that the use of serum intra thecally is contra-indicated; also he insists that while his patients received massive doses of antitoxin, that if there is good wound control the dose of the antitoxin may be cut down.

Dietrich (14) the bitter foe of the intra thecal route of injection reports 15 cases in children from 1921-32 with a mortality of 80 percent and 13 cases from 1933-38 with a mortality of 8 percent. The decrease in mortality, Dietrich explains, is due to the change in the method of treatment. During the period of 1921-32 serum was given intra thecally and intra venously, and only a moderate amount of sedation was given; in the latter group (1933-38) the intra thecal route was not used at all, and only one intra venous injection was used per patient and this injection was given with epinephrin. All of those patients that died (1921-32) died 36 hours after treatment was started, with the previously mentioned "bulbar polio." Dietrich describes this type of reaction in the following way: "there is coma, an increased fever, tachycardia, stertorous and irregular respiration, there is a cessation of tonic

convulsions, an ashen complexion,profuse perspiration, with cold and mottled extremities. The cause ofdeath is a cerebral and medullary edema. The author states that there were four cases in the latter group who showed this severe bulbar reaction, one of the patients died; the other three patients received hypertonic sucrose solution, which apparently relieved the edema in the brain and thereby saved their lives. In the cases (4) that received only intra muscular injection there were no reactions and all the patients lived. Dietrich believes that the "bulbar reaction" is more likely to occur in children, hence he theorizes that children may react differently to horse serum than adults, or that the arachnoid space in children is too small; the latter point was not enlarged on by the author. In four cases that had compound fractures, three of the cases had received 1,500 units of antitoxin prophylactically, but all three of these patients developed tetanus and died; therefore Dietrich assumes that 1,500 units is not adequate protection in cases of severe compound fractures. In spite of Abel's (7) findings Dietrich maintaines that it is impossible to neutralize fixed toxin, that only circulating toxin is neutralized, hence the intra venous route is the best, but it must be used with caution, and then only once. The remainder of antitoxin should be given intra muscularly, 10-20,000 units per day for two to four days.

Coinciding with Dietrich's belief that the intra thecal route should be discarded Speath (38) reports a total difference of 9 percent in mortality when the intra thecal route was not

used. Thirty-three patients were treated intra thecally, intra venously, and intra muscularly; also thirty-three patients were treated intra venously and intra muscularly. There was noted a very significant decrease in mortality in the more severe cases (incubation period of ten days or less) when the intra thecal route was not used. Speath noted that 21 out of the 45 patients that had a fever died, while the 21 that had a normal temperature lived; so he assumes that the temperature curve is prognostic if the cause is known; it is not necessarily the level of the temperature that is prognostic. An increase in the temperature may be due to infection if so the tatnus is usually more virulent in nature, also a rise in temperature may be due to intra thecal injections, and the temperature rise in this case may herald an approaching "bulbar reaction.".

Speath is of the opinion that only a moderate dose of antitoxin is necessary, for in a series of 169 cases that he analyzed as mild, moderate, and severe he found that the amount of antitoxin bore no relation to the mortality (19). Speath estimates that 35-50,000 units of antitoxin is all that is necessary. The following is a chart reproduced from Speath's article (19).

	24 hrs.				48 hrs.				Entire Stay			
	Recovered		Deaths		Recovered		Deaths		Recovered		Deaths	
	No.	Dose	No.	Dose	No.	Dose	No.	Dose	No.	Dose	No.	Dose
Mild	32	37.7			32	48.2			32	91.0		
Moderate	26	35.2	8	41.4	23	56.1	6	73.5	26	119.4	8	103.9
Severe	5	31.2	98	37.0	5	43.2	36	66.2	5	78.2	98	55.4
	63	35.8	106	37.4	60	50.8	42	56.8	63	101.7	106	58.1

Vener and Bower (13) recommend that methenamine be given along with anti-toxin because this drug allows a greater permeability of the choroid plexus to serum; by forming formic acid it acts as an anti-septic; may alter colloids in nerve cells; may have some unexplained action on the toxin. The first reason given, according to the author is probably the best.

I believe it would be of distinct value to report the method of treatment used by Vener and Bower (13) for they had a mortality rate of 19% in 100 cases of adult tetanus. This is an excellent record. As will be seen later, the treatment makes use of the cisternal puncture, and because a goodly position of this paper has been dedicated to the dire results obtained by intra-thecal and cisternal administration of anti-toxin, it probably seems strange that the technique that has been condemned should bring such excellent results; however, it must be remembered that these 100 cases were all adults, and as Dietrich (14) brought out, the cisternal and intra-thecal routes are much more dangerous in children than in adults. Also Vener and Bower omitted the cisternal route immediately if there were signs of any reaction. The following is the technique used by Vener and Bower (13):

1. A complete history, physical examination, and a horse serum test are given at first.

2. Ten to thirty grains of chloral hydrate, depending on weight of patient. Pheno barbitol (3-5 grs.) may be given intravenously if more sedative is needed. However, it is best to avoid a too deep narcosis, for adverse metabolic changes may take place.

3. About 2 hours after the above, 60,000 units of anti-toxin is injected intra-muscularly above the wound, 20,000 units is given around the wound. Then the wound is debrided under local anaesthesia.

4. Then 3 hours later 20,000 units is given cisternally by gravity, serum should be at body temperature. The next step is not undertaken until the rectal temperature is 102°F or less.

5. 40,000 units in 300-500 cc. of saline is given intra-venously, this injection should not take less than one hour to give, and 3 cc. of epinephrine is given the patient 5 minutes before injection, mid-way of the injection, and at the completion of the injection. The author recommends that .1 cc. of anti-toxin (or horse serum) be put in 9.9 cc. of saline and given intra-venously, blood pressure readings are then taken every 5 minutes, if the blood pressure does not drop 20 points in 20 minutes the patient is not sensitive to intravenous serum. Serum given intra-venously should be luke-warm.

6. Then 2 hours after the above 15 grains of methenamine is given intra-venously.

7. One hour later, 20,000 units of serum intra-venously; this step is not to be taken if there has been any previous reaction.

8. Twelve hours later 40,000 units intra-muscularly. If it has been necessary to omit the intra-venous injection then give 60,000 units.

9. Twelve hours later 15 grs. of methenamine is given intra-venously. This step is carried twelve hours after each intra-muscular injection.

A total dose of 200,000 units has now been given in about 36 hours. Subsequent serum dose is 1500 units subcutaneously every 4 or 5 days if the patient needs it, the patient should not receive more than 230,000 units; however, if subsequent surgery must be done continue 1500 units intra-muscularly every 4-5 days for two weeks after surgery. If the patient should prove sensitive to horse serum, the patient is

desensitized, and two intra-muscular injections of 200,000 units each are given, the intra-venous and cisternal routes are omitted.

This, in short, is the technique that Vener and Bower used in getting such an excellent mortality rate; the author insists that excellent general treatment is essential to saving life. Patient's position should be changed frequently, if convulsions can be avoided, to prevent pneumonia; also oral hygiene should be maintained for very often sinusitis develops if mouth is not kept clean and patient is under deep sedation. Vener and Bower intimate that a nurse who has had experience with tetanus cases is as valuable as the anti-toxin.

Tetanus, like most of the other ills of man has at one time or another been treated with one of the sulfonamide products with varying success. Penrod and Knoll (39) in their report of a death from tetanus treated with sulfamilamide and anti-toxin state that Osgood and Powell (1938) could not demonstrate any effect of the sulfonamides on one m.l.d. in guinea pigs. Sharp (1939) reported five consecutive recoveries when treated with sulfonamides. Blouton (1939) reported one case recovered when treated with sulfapyradine. Lemere and Arnason (40) report a recurrent attack of tetanus that occurred 18 days after dismissal from hospital was cured with azosulfamide. The author of this latter article inferred that the foci was not obliterated during the first treatment, hence more toxin was put out, and that the azosulfamide obliterated the foci. The second attack was completely aborted in five days time.

There certainly has not been enough clinical work done with the sulfonamide products in tetanus to warrant any general conclusions at this time.

Heersema (41) reports a case wherein a patient had received 100,000 units of serum with adequate sedation; yet the patient was not getting any better so it was thought that if the patient could be given heat treatments the heat might act as a catalyst and increase the velocity in neutralizing the toxin. A total of twelve heat treatments were given to this patient, and with each treatment the symptoms were greatly alleviated. The patient became progressively better and was finally dismissed the twenty-fifth day. While these heat treatments were being given, it was noted that there was blood in the patient's stools; the only way this could be accounted for was that the increased heat caused a more rapid combination of vitamin C with the toxin (all infectious diseases cause a low vitamin C) and because of this deficiency there was some bleeding from the bowel; this of course is entirely theoretical. I do not believe that heat treatments should be a part of the routine treatments of tetanus, but if a tetanus case is not responding to the usual treatment, then I believe the use of heat is justified.

I have neglected to mention tetanus neo-natorum, because fortunately it is very rare in this country. When it does occur it carries a 90-95% mortality. The location of the infection is usually in the umbilical stump. Mowsky (42) reports the successful

treatment of a case of tetanus neo-natorum with 10,000 units of serum intra-muscularly every day for ten days. Nembutal 3/4 grain every three hours was used for sedation. There were no convulsions after the fourth day of treatment, the patient was dismissed on the fourteenth day.

Mitchell (43) reports one case successfully treated with curarine and anti-toxin. The curarine was given sub-cutaneously, the doseage beginning at.1 mg. every four hours, gradually increasing dose until it reached.5 mg every four hours. In this case it was not necessary to use artificial respiration. West (43) reports 10 cases that were treated with curarine in which 9 of the cases died. West states that those patients that received the curarine intra-venously showed the best improvement; most of these cases had incubation periods of under seven days; consequently, they were all virulent types of tetanus; however, these patients lived longer than expected when given intra-venous curarine. However, West believes that curarine is a dangerous drug because of the "respiratory spasm" that may be produced. Isacson and Swenson (45) attempted to treat a case of tetanus with intra-venous and intra-muscular curare. Ninety milligrams were given intra-venously over a period of about 3 hours, forty milligrams were given intramuscularly. The patient became completely relaxed, an artificial respiration was used; however, the relaxation was not maintained long enough, and the patient had a severe convulsion when an attempt was made to enter a vein, he developed an aspiration pneumonia and died.

There is no doubt in my mind that curare would be of great benefit in tetanus, but curare is very difficult to standardize, hence the toxic dose is very hard to determine, and artificial respirators are not always conveniently handy; so while curare may be of some value, it is not practical as yet.

One of the most difficult situations that must be met in the treatment of tetanus is the treatment of the serum sensitive patient. Schaeffer and Mevers (46) using a new despicated anti serum made by Parke Davis successfully treated a patient who was very sensitive to horse serum; developed a severe asthma when only .1cc. of horse serum was given intra-cutaneously. This new serum was given .1 cc. sub-cutaneously, and the dose was gradually worked up to 10 cc. (undiluted) intravenously over a period of twenty-four hours. Thereafter, the patient was given 10 cc. (undiluted) intra-venously every twelve hours until 1400 cc. of serum had been given. The only reaction was an occasional slight chill, but one month later a mild urticaria developed. One year later this same patient was skin tested with this new serum, and he showed a wheal of 1.2 cm. with an area of erythema 3.0 cm. The old type of serum showed a wheal of 1.8 cm. with an area of erythema 6.0 cm.

This new type of serum is made by Parke Davis. The antitoxin is diluted with distilled water containing phenol; this solution is buffered to a Ph of 3.8 after which the diastase is added. This mixture is then incubated at 37° C. Filter the

solution, adjust Ph to 7, the anti-toxic globulin is salted out, the precipitated globulin is dialyzed, then diluted until the desired percentage of nitrogen is present. The anti-toxin is then made iso-tonic, and filtered again.

Apparently this digestive method is of some value in preventing serum reactions; however, its true value cannot be estimated until the results of its use are reported in several hundred cases.

The successful treatment of tetanus depends upon the ability of the clinician to evaluate the degree of tetanus present at the time he sees the patient, and the length of the incubation period should be ascertained, if possible; by knowing these two things,-the intensity of the treatment and the prognosis is determined.

Before instituting treatment with anti-tetanic serum skin tests with horse serum should be done. And if it is necessary to give anti-serum intra-venously it should be done cautiously preceding the injection with epinephrine.

It is my conclusion that the safest way to give anti-toxin is intra-muscularly. If the degree of tetanus is only slight then I believe it is best to give only one injection intra-venously, the remainder of the serum should be given intra-muscularly. In the more severe type of tetanus it is necessary to give intra-venous injections more than once, but I do not believe the intra-venous method should be used more than once in a twelve-hour period, the serum should be given very slowly.

The intra-thecal method should not be used, particularly in children. If it is used at all, one injection is all that I think should be given, and the amount should not be over 10,000 units.

It is my belief that anti-toxin should be given until the symptoms and signs of tetanus have disappeared. For it is impossible to tell when the foci of the toxin is obliterated, and it may be true that fixed toxin is neutralized by adequate amounts of anti-toxin, whether this last statement is true, I do not know, but there is enough experimental evidence in its favor that would cause me to be conscious stricken if I did not attempt to neutralize the fixed toxin.

The importance of sedation cannot be over emphasized. The sedatives should not "knock out" the cough reflex or respiratory center. I have chosen anertin (rectally) augmented by oral (if possible) doses of one of the barbiturates, the latter to be in rather small doses.

The patient should be attended, preferably by nurses who have had experience with tetanus patients and there should be a nurse in attendance day and night. Absolute quiet is essential. The patient should not be disturbed more than necessary. Adequate fluid intake should be maintained. Feeding the patient is not too important; a tetanus victim does not die of starvation; however a light diet should be maintained.

If there is no response to the usual treatment of tetanus, the prognosis is bad. However, the use of heat treatments or curare' may bring on a favorable outcome, at least they would be worth trying.

PART IV

IMMUNOLOGY IN TETANUS

IMMUNOLOGY IN TETANUS

While there is still a variety of opinions as to the best method of active treatment in tetanus; everyone is agreed that active immunization has proven itself the deciding factor in the elimination of tetanus.

Jordan and Halperin (47) in their article of March 1941 state that the attempt to immunize actively against tetanus probably came out of a similar effort put forth against diphtheria by Ramon, Paris; Glenny and Hopkins, London; and Park, New York; who began by treating diphtheria toxin with formaldehyde. This work was based on the fundamental work of Salkowski (1896) and by Lowenstein and von Eisler, who found that formaldehyde treated toxins lost their toxicity but retained their anti-genic properties. It was in 1924 that Ramon prepared a tetanus toxoid with formaldehyde and heat; one year later he collaborated with Descombey and prepared fatal doses of toxin in such a manner that five to ten cubic centimeters of the toxin would not cause symptoms. At the present time Jordan and Halperin recommend Campbell's method of preparing toxoid, which is as follows: Organisms are harvested on Witte's peptone broth for about 5-14 days; toxin is obtained from a filtrate of the culture and the lethal dose is determined. The filtrate is then put through pulp paper filters and Berkfeld N candles; next a 3% formalin solution is added, and the mixture is incubated at 37°C for three weeks. The substance is regarded as

a complete toxoid when 5 cc. in a guinea pig produces no symptoms, this means that the animal must be kept under observation for three weeks. When the toxoid is ready for use, it is again put through Berkfeld N candles and submitted to sterility tests. Glenny, Pope, Waddington, and Wallace (1926) found that the anti-genic property of the toxoid was greatly increased when the toxoid was precipitated with .1-1% potassium alum, and at the present time as high as 2% alum is used. In determining the amount of alum needed, various amounts of alum are added to fixed quantities of the toxoid, the supernatant fluid of each quantity is then tested for toxoid, and by this method the smallest amount of alum needed to precipitate out the toxoid completely is determined. The correct proportion of alum necessary is then added to the bulk of the toxoid, and it is allowed to stand over night. The precipitate is then washed with a sterile solution of sodium chloride or sodium phosphate and an anti-septic is added. This alum precipitated toxoid is reported by Hayden and Hall (1938) as being thermostable; hence, it can be carried by the armed forces in the field. It is of interest to note that Ramon reports that the anti-genic value of toxoid may be greatly enhanced by adding tapioca to the toxoid.

Does one attack of tetanus give a complete immunity? Vener and Bower (48) report that there have been reported only about 5 cases of tetanus developing in patients who have previously had tetanus, and these two men add a case to this list in which tetanus developed in a patient three and one-half years after the first attack. The authors believe that three and one-half years is long enough to

insure the fact that this was not a recurring attack of tetanus. In view of this one case and the five others mentioned, one cannot state that an absolute immunity is conferred on the tetanus victim, but recurrences are so rare, that it must be assumed that at least some immunity results from an attack of tetanus.

Naturally before tetanus toxoid was used on humans a great many animal experiments were carried out. Among them some excellent work was done by Otten and Hennemann (49), these men attempted to determine the effect of giving toxoid and tetanus serum together. The experiment was carried out on guinea pigs; one cubic centimeter of a 1:10 dilution of toxoid and 50 units of tetanic serum were used. These two were given at various time intervals and together; and the anti-toxin levels were determined in the blood. The reason such an experiment was carried on is that it takes about four to six weeks for a sufficiently high anti-toxin titer to develop when only toxoid is used, so in order to bridge that gap it was thought that serum should be given. However, Otten and Hennemann showed that the serum in the blood stream tends to reduce and retard the active response to toxoid, also when the two were combined the anti-toxin in blood stream was lower than if just either the toxoid or serum was used alone. This so-called inhibitive action is believed to be due to the anti-toxin itself as well as the horse serum, the former is probably the most important factor although the exact reaction has never been determined.

While this so-called active-passive type of immunization

is not used in this country, Ramon (62) in France believes that the serum should be given at the same time as the first injection of toxoid to create a passive immunity while the active immunity is being built up. The technique involves giving 150,000 units of anti-toxin with the first dose of 2 cc. of toxoid (plain) then the toxoid is increased by 2 cc. every 6 days until three injections have been given. In this manner Ramon says he created a passive immunity immediately followed by an active immunity. Ramon recommends that a booster dose be given once a year of 2 cc. of toxoid.

Zuger, Greenwald, and Gerber (50) conducted experiments on guinea pigs in order to prove their contention that in a actively immunized animal an infection with tetanus spores will increase the anti-genic titer of the blood. Guinea pigs were actively immunized with the tetanus toxoid, then given tetanus spores. Subsequent titrations of blood showed that on the seventh day after the spores were given a small rise in titer was noted, particularly in those guinea pigs that showed no symptoms or in those guinea pigs that eventually got well. A greater rise in titer was noted on the eighth to tenth day. If toxin were given instead of the spores, there was a definite rise in titer by the 4-5 day. There is no evidence that the rise in titer influences the clinical course of the disease in any way. In general the animals that were going to die showed no change in titer by the sixth day, while those animals that were going to live showed an increase in titer by the thirteenth day.

In an attempt to develop a toxoid with a higher antigenic

value, Penfold, Toehurst, and Wilson (51) believed that this could be done by concentrating the toxin that the toxoid was made from. This was done by adding 25% solid sodium chloride, then adding a 2% solution of glacial acetic acid. Mixture is then left standing for 16-18 hours at room temperature. The resulting precipitate is centrifuged or filtered. The total yield from the toxoid is about 50%. It was also thought that this concentrating process would remove the hemolysins from the toxins, and by titrating with sheep red blood cells, it was proven that the hemolysins were destroyed if tryptic broth was used as a diluent; the hemolysins were not destroyed if saline was used as a diluent. The method used in determining if the hemolysins were present was to inject the concentrated toxin in guinea pigs and then watch for a haemoglobinuria. It was also determined that this concentrated process eliminated a necrotizing toxin. This was proven by injecting crude toxin and concentrated toxin into the abdominal wall of the guinea pig and then making a microscopic examination. While it was true that some of the toxic properties were removed by concentrating the toxin, the anti genic quality of the resulting toxoid was not enhanced by concentrating the toxin one bit. The toxoid made from the concentrated toxin was used to immunize guinea pigs and cats, and it was found that these animals could not withstand any more lethal doses of tetanus toxin than those guinea pigs and cats that were immunized with the crude toxoid.

When it was finally proven by animal experiments that

tetanus toxoid had little, if any, toxic properties as compared to the tetanus anti-serum; the technique of immunizing was worked out by using various procedures in large groups of people, then determining their blood titers at various intervals.

In 1935, Sneath and Kerslake (52) immunized twenty-seven persons by giving three doses of the plain toxoid, one cubic centimeter per dose at two week intervals. One year after the first injection, the blood titers varied from .5 to .001 units of antigen. A secondary stimulus of the plain toxoid given at the time of the titration boosted the titers up to .1 to 5 units in seven days time. It must be remembered that Sneath and Kersloke (52) were using the plain toxoid; the alum precipitated toxoid would have given higher titers as will be shown later.

In another series of 12 persons, who were immunized by Sneath and Kerslake (53) in the same manner mentioned before, showed by blood titrations at the end of two years time that the titer levels varied from .1-.001, which were the same as the levels at the end of one year. A booster shot of 1 cc. of toxoid at this time (2 years) raised all of the blood levels from .1 to 10 units within seven days.

The United States Navy was the first large organization in this country to begin mass immunization with tetanus toxoid (plain). Hall (86) completely immunized 47 men, and 31 out of this group received a "booster dose." The primary doses were 2 injections of 1 cc. each; some were given at four week intervals,

others were given at 8 week intervals. Titrations done four weeks after the first injection averaged .025 units; after an 8-week interval the average titer was .055-.1 units. Consequently, it was concluded that the longer the interval between the two primary injections, the higher the titer. "Booster doses" given about 1 year after the primary immunization revealed that the average titer was 2.5-50 units. No matter what the interval between the primary injections, the "booster dose" always gave a substantial "jump" in the blood titer.

In June 1941, McBryde (54) immunized 94 colored children with 2 injections of plain toxoid, 1cc. at each injection 73 days apart. Forty-five days after the first injection, 75 of the children had blood titers that averaged .01-.1. Thirteen had more than .1 units, two had .25 units. One hundred twenty-seven days after the first injection, all of the blood titers averaged between .1 and 5.

Gold (55) in attempting to ascertain if it was necessary to use 1 cc. of plain toxoid at each injection; immunized 16 persons with two injections of .5cc. at 92 day intervals, also he immunized 18 persons with two injections of 1 cc. at a 92 day interval. Blood titrations taken after first and second injection showed that those who received the 1 cc. injection had the highest titers. As will be seen later, when the new alum precipitated toxoid is used, a .5cc. injection is as adequate as the 1 cc. injection.

Gold (56) began using the new alum precipitated toxoid in 1936. Fifty adults were immunized with two .5 cc. injections at 645 day intervals. When the second injection was given, two years after the first injection, a titer of .1 unit per cubic centimeter developed in 5-14 days. The duration of this protective level (.1 unit/cc) varies, according to Gold, from 90 days to 2 years. If a "booster dose" is given the so-called protective level is not reached for about 5-7 days. (The protective level of anti-toxin is not just an arbitrary figure because Cowles (57) working with guinea pigs showed that a blood level of .1 unit per cc. was sufficient to protect the guinea pig from infection; also Cowles showed that 1500 units injected into man gave a blood titer of never below .1 units; consequently 1500 units became the usual prophylactic dose of anti-toxin.) Gold (56) also showed that the protective level that is reached after the "booster dose" lasts from 3-6 months.

In 1939 Gold (58) thought that perhaps he could get higher blood titer if he mixed the plain and alum precipitated toxoids together, so he immunized 32 individuals in the following manner:

A. 12 persons- 3 injections of plain toxoid 1 cc. 1 month intervals

B. 12 persons- 3 injections plain and alum toxoid 1 cc. 1 month intervals

C. 8 persons- 2 injections alum toxoid 146 days apart

In C. one-half got .5 cc., other one-half received 1 cc. In titrating the serum of the above various groups, Gold found that when the alum toxoid was used above, the titers were higher after

the first and second injections. Gold also maintains that this experiment shows that the longer the interval between the first and second injection, the higher the blood titer.

In February of 1940, Gold (59) titrated the blood of thirty-four persons after they had received their "booster doses." The interval after the last injection of the primary immunization series varied from 272 to 359 days. All of these persons were titrated before their "booster dose" and all but two persons showed less than .1 unit per cc. It was found, as stated previously, that it took 5-7 days to raise the titer to a protective level after the "booster dose." In seven of these persons, the titer was increased fifty times the level before the "booster dose." Fourteen showed a blood level of .1 unit eighteen months after "booster dose", while sixteen showed less than .1 unit.

In order to get around the inconvenience of having to inject the "booster doses", Gold (60) developed a toxoid topagen that could be placed in the nose. One tenth of a cubic centimeter of topagen placed in each nostril on 3 successive days will raise the titer in the blood from below .1 unit to .1 and above within 7-9 days, where this titer will remain for several months. It was found in experimental work done on 145 persons, that if this nasal procedure was carried out every six months an adequate protective level was maintained. When this nasal topagen was substituted for the injection procedure in the primary immunization, it was not successful. However, Gold recommends this nasal topagen

for the "booster dose", for it requires no syringe, hence it can be done by the person himself in the home or on the battlefield. Also when the nasal route is used, there is very little reaction --only some burning in the nose and a bad taste in the mouth for a little while.

Bergey, Brown and Etris (61) believe that children have a tendency to develop higher titers than adults because of the following experiment:

30 persons between 18 and 20 years

1 cc. alum toxoid, 90 days later showed .001-.04 units

1 cc. alum toxoid, 90 days after 1st injection, .1-9 units/cc 30 days later.

44 persons between 30 and 50 years

1 cc. alum toxoid, 90 days later titer was .0005-.01 units

1 cc. alum toxoid, 90 days after 1st injection, .01-4 units 15 days later

As seen in the above, not only does the older person develop a lower blood titer than the younger person, but the titer "falls off" faster in the older age group. Consequently, these authors conclude that it may be necessary to give the primary immunization injections in 3 doses to the older group. Bergey, Brown and Etris (61) by experimenting with guinea pigs showed that the protective value of the toxoid is not all in the humors of the body, because in a guinea pig with a blood titer of .2 units/cc. this guinea pig should neutralize 6000 lethal doses of toxin; however, a guinea pig with such a titer can withstand 15,000 lethal doses of toxin; so it is concluded that the non-circulating immunity is 1 1/2 times as great as the circulating immunity.

Marvell and Parish (63) immunized the entire personnel staff at the Wellcome Laboratories in England, and from their titrational findings they concluded that perhaps there is some sex differences in the response to the toxoid. The method used was to give three injections of 1 cc., 2 cc., 3 cc. at 2 or 3 week intervals, followed by a booster dose of 2 cc. at the end of one year. Their findings agreed with other investigators that it takes at least two primary injections to get a protective titer, and that a "booster dose" is necessary at least once a year to keep the protective level. But it was noted in titrations done after the primary immunization that twenty-one males out of thirty-two had titers of .2 units or below, and eleven had titers above .2 units. Six females out of twenty-nine had titers of .2 units or below, while twenty-three had titers above .2 units. These figures are significant, for when the Yates correction factor is worked out, P is less than .001. Marvell and Parish also point out that according to the 1927 statistics, 105 boys died of tetanus as compared to the 57 girls that died. All of these deaths occurred between the ages of 1 week and 1 year. Also in the age group of 1 week to 1 year from 1901-9, 25 boys died as compared to 4 girls. Since there is no appreciable difference in risk between the ages of 1 week and 1 year, there evidently is a greater in-born immunity to tetanus in the female. In this group immunized by Marvell and Parish (63), there were several persons who spent most of their time working around horses, it

was contended that these persons were constantly in greater contact with the Clostridium tetani than any one else; yet their titers were no higher than those who did not work around horses.

At the present time tetanus toxoid is combined with diphtheria toxoid. Some authorities believe that the combination of the two toxoids give a resulting higher titer than if either were used alone, while other investigators disagree. However, it is agreed among all those who have studied the subject that the diphtheria and tetanus toxoids do not inhibit each other.

Jones and Moss (64) immunized forty-one medical students by injecting two .5 cc. doses of combined tetanus and diphtheria toxoids at one month intervals, with the exception of 6 students who received only .25 cc. on second injection because they had shown an allergic reaction to the first injection; the authors believed that the allergic reactions were due to the protein in the diphtheria toxoid. One month after the primary immunization the blood titers varied from 1/2-1/60 of a unit, and interestingly enough only one of the students that received .25 cc. of toxoid on record injection showed a titer of 1/60 unit. Two months after the primary injection the blood titers varied from 1/10 to 5. Those that had received the .25 cc. of toxoid--two had .1 units/cc, two had .2 units/cc, while one had 5 units/cc. From these figures, the author assumed that perhaps those that are sensitive to the toxoid may develop a higher titer; or perhaps it is possible that it is not necessary to give .5 cc; perhaps a smaller dose would be just

as valuable. Jones and Moss state in this article that they believe that the combined toxoids tend to give a higher titer than if either one is used alone; however, these authors present no evidence for their belief. In another article by Jones and Moss (65) they intimate that the medical students just mentioned would have had higher blood titers if the interval between the first two injections was two to three months instead of the one month.

Biger and Werner (66) immunized 240 infants and children against tetanus, using various methods, and they found that the best method was 3 injections of .5 cc. each every three months, as compared to giving 2 injections of 1 cc. every three months. By using the former method, the average titer three months after the primary immunization is no lower than .5 units, and the average titer stays higher for a period of six months than if the latter method was used. However, by the end of a year, no matter what method of primary immunization was used, the average titer is the same, and as stated before the "booster dose" raises the titer to a protective level no matter what the method of primary immunization but the high titer obtained after the booster dose will remain longer if the primary interval is longer. Biger and Werner (66) tried intra dermal immunization on thirty-five out of the group of 240, but it was not successful.

In concluding this section of my paper, I believe that Von Canon's composite table of the titrational statistics of Sacquepee, Bergey, Sneath, McBryde, Jones, Moss, and Gold (all

who have been mentioned in this paper) gives an excellent review as to the comparison of alum and plain toxoid, the doseage of toxoid, and the interval between injections:

Titers	Time of Titration After Primary Immunization	Plain Toxoid	Alum Toxoid
.01 unit or above	1-2 months	86%	100%
.01 " " "	6 months	96%	95%
.1 " " "	1-2 months	67%	97%
.1 " " "	6 months	53%	37%
.25 " " "	1-2 months	12%	72%
.25 " " "	6 months	4%	6%

Doses

Alum Toxoid .5-2 cc. in 2 injections 1 month to 8 weeks apart

Plain Toxoid 2.5-4.5cc. in 3 injections, average once a month

Generally speaking, the use of tetanus toxoid causes very little or no allergic reaction. Biger and Werner (66) report that there is usually a little stinging and burning over the injected area; may be a lump present for several days. Also a mild malaise with fever is not uncommon, lasting only about twenty-four hours. Urticarial rashes are quite rare, and when they do occur, they readily respond to epinephrine.

There should be no hesitancy to immunize allergic children, for Gold (68) successfully immunized a large number of allergic children to tetanus, and he found that the average titer in these allergic children was no higher than in those who were not allergic.

Gold maintains in this article that if some reaction does develop it is probably due to some impurity in the toxoid. For example, Parish and Oakley (69) reported a case of anaphylaxis resulting from the second injection of tetanus toxoid; however, subsequent intra-dermal tests done on the patient after being treated with epinephrin showed that the element at fault was Witte's peptone, the media which the Clostridium tetani was cultured from. Whittingham (70) reports 2 cases of anaphylaxis from tetanus toxoid out of 61,402 immunizations, and these two cases were later proved to be sensitive to Witte's peptone broth.

Cooke, Hampton and Shaw (71) report four out of twenty-five cases wherein the first injection gave an allergic reaction (hives). These three men carried out extensive intra-dermal tests on these four patients with all of the various components that make up the tetanus toxoid, and they found that the primary and secondary proteoses that are found in the various peptone broths were to blame. Consequently, it was recommended that scratch tests should be done before each injection, and if possible some way should be perfected wherein the media could be purified.

Hall (72) of the United States Navy reports that in 1938 twenty-three hundred men were immunized at the United States Naval Academy; after the first injection 8 men reported very sore arms, 5 had fever and malaise. After the second injection (given to 1800 men), 38 had sore arms, 7 had fever and malaise, 4 had urticaria, and there was one anaphylactic shock. On examination of the

toxoid that was used, there was found to be a large quantity of protein present, as determined by the nitrogen present and the various protein tests. Later another brand of toxoid was used and 793 men were successfully immunized, and there was only one case of fever and malaise.

Drawing my conclusions from the variety of facts and figures presented in this section of my paper, I am convinced that the present method of immunization against tetanus is of real value, but I do not think one should feel too safe merely because a person has been immunized, for the degree of antigenic titer in the human organism depends upon the inherent ability of that organism to manufacture anti-toxin, and in the majority of the titrational experiments mentioned there was usually one individual who did not respond at all to the toxoid, however this type of individual is much too rare to affect the general use of toxoid. Nevertheless, there are some investigators who recommend that an immunized person should have tetanus serum as well as a booster dose when they suffer some severe traumatic injury.

One-tenth unit of antitoxin per cubic centimeter has been set as the minimal protective titer (based on Cowle's work (57) but I do not believe such an arbitrary standard should be set; for as Cowle stated himself, it is impossible to determine how much toxin is likely to be liberated in a single case of tetanus, therefore, the higher the anti-toxin titer in the blood stream the better.

It is my contention that all children should be

immunized against tetanus; preferably before they reach the more active states of childhood. In producing the primary immunization, the alum precipitated toxoid should be used, and the interval between the first and second dose should not be shorter than six weeks. This time interval is important for it is during this time that the cells in the reticulo endothelial system are building up a sensitivity to the toxoid so they will be able to produce anti-toxin when they are again stimulated or "boosted" by another injection of the toxoid. It is only theoretical that it is the reticulo endothelial cells that are responsible for the production of anti-toxin; perhaps all of the body tissues are capable of responding to the toxoid. The dose of the alum precipitated toxoid varies between .5 and 1 cc; best results were obtained when .5 cc was given sub-cutaneously for three injections spaced at three month intervals. It is absolutely necessary to give a booster dose of .5-1 cc of toxoid to most persons at least once a year. In children I believe that Gold's topagen intra-nasally every 6 months is an excellent way of keeping the titer at a protective level.

In cases of injury where there is danger of tetanus, anti-tetanus serum should be given to every one who has not completed his primary injections for immunization, and if the injury is such that tetanus is more than likely to occur I believe that tetanus serum should be given, even if the person is immunized, along with the usual booster dose.

PART V

VARIOUS REACTIONS RESULTING FROM PROPHYLACTIC SERUM INJECTIONS, INCLUDING A REPORT ON 389 PROPHYLACTIC INJECTIONS OF TETANUS ANTI SERUM

VARIOUS REACTIONS RESULTING FROM PROPHYLACTIC SERUM INJECTIONS, INCLUDING A REPORT ON 369 PROPHYLACTIC INJECTIONS OF TETANUS ANTI SERUM

The usual prophylactic procedure in preventing tetanus is to inject subcutaneously 1500 units of tetanus anti-toxin. With the present day highly-purified anti-toxin this procedure is relatively safe, but in some instances there will be reactions in spite of negative skin tests.

Lyall and Murdick (73) in reviewing one thousand cases that had received 1500 units of anti-toxin found that 15.2% developed a generalized serum reaction, and that only 3.5% of this group developed within 24 hours. Only 1/4 of the serum reaction could be counted as severe, that is, there was malaise, fever, urticaria, and very sore arms. There were only two cases that showed alarming reactions, that is some impairment of respiratory function. Twelve and one-half percent of the group had minor localized reactions around the site of injection. It was noted that the incidence of reactions tended to drop when the potency of the serum was increased and the protein content decreased. Repurification of the serum seemed to have little effect on decreasing the number of reactions.

Newell and McVea (74) in reporting 500 injections of prophylactic tetanus serum stated that 92 patients had had tetanus serum before and that 9 of these patients recalled having had some reaction. The skin tests on these 92 patients showed that 55 were positive and 37 were negative; therefore obviously not every one who receives horse serum becomes sensitive to the serum at least

the sensitivity does not last or the intra-dermal skin test does not always show positive in a serum sensitive patient. In this series of 500 cases only 59 showed some sort of a reaction, local or general, and 30% of the 59 had previously received horse serum in some form. There was only one case of anaphylactic shock in the whole group of 500. Fifty-one developed a delayed local reaction, 22 developed a delayed general reaction. For the most part, the reaction consisted of red, swollen, sore arm, and in some cases an associated adenitis. Four percent (22) developed a true serum sickness with urticaria on the fifth to eight day after the injection; only two of the cases of serum sickness were severe, with edema of face, eyelids, extremities, and loss of weight. The serum sickness cases were successfully treated with sedation, baths, ephedrine, epinephrine, phenolated calamine lotion. From the data collected from these 500 cases the authors conclude that a reaction from horse serum is most likely to occur in those who have ~~formerly~~: (1) received therapeutic serum, (2) asthmatic patients, (3) formerly received prophylactic tetanus serum, (4) those who recall a reaction from horse serum. Several different brands of tetanus anti-toxin were used, and it was found that not one brand could be blamed for all of the reactions; therefore, it was assumed that it is the individual alone who is responsible for the reaction.

The layman who has received tetanus anti-toxin is likely to blame all of his subsequent ills on the injection; usually his claims are unfounded. But in 1937 Rhodes (75) reported a case of

hematuria resulting from an injection of tetanus anti-serum. The person involved was a male, 21 years old; 2 days after he received 1500 units of anti-toxin he noticed bright red blood in his urine. Cystoscopic examination showed that the blood came only from the right ureter. There were no other systemic findings, no symptoms, and no history of allergy. All tests for tuberculosis were negative. In one week's time, the urine was absolutely clear; the hematuria has never returned and the patient was in perfectly good health one year later. The author believes that the hematuria was due to a right renal allergy. This assumption is certainly debatable, but since no other cause could be located, and since the hematuria stopped so suddenly the author believes that renal sensitivity to the horse serum was responsible. There have been no cases of this sort reported in this country; however, the author mentions a few cases have been reported in foreign literature. I bring this case into my thesis merely as an oddity, and to illustrate that anti-tetanus serum often acts in strange and unaccountable ways.

A reaction from tetanus anti-toxin that used to be considered rare is neuritis. More and more cases of neuritis from serum therapy are appearing in the literature. The usual location of the neuritis is in the brachial plexus; however, it can occur elsewhere. Cutter (76) in 1936 reported the first case of auditory nerve involvement from tetanus serum. This patient had received a total of 125,000 units intra-muscularly, intra-venously, and intra-thecally for an active case of tetanus. About eight days

after receiving all this serum, he noticed that he began to lose his hearing, developed a generalized rash, stiff neck, and he became irrational. It was found that 61% of his hearing was gone in the right ear, and 69% was gone in the left ear. Two months later he had only a 9% hearing loss in right ear, and a 21% hearing loss in the left ear. MacCready (77) later reported a patient who had received 3000 units of tetanus anti-toxin prophylactically; 10 days after the injection the patient developed a serum sickness, with vertigo and fever. Four days later a 45% hearing loss developed in both ears; also there was a definite vestibular impairment, as the caloric tests were negative. The patient had not shown any signs of improvement over the last year (1938). MacCready says in his article that only two other cases of eighth nerve involvement have been reported, but both of these cases involved the treatment of tetanus.

Neffson (78) reports the case of a patient who had received 1500 units of anti-toxin prophylactically, and three days later developed a urticaria and pain in joints. Also at this time the left vocal cord became paralyzed; there was a loss of left laryngeal sensation, the left pupil became dilated, there was a paresis of the right face, and there was a left positive Babinski. Neffson believes that the cause of this laryngeal paralysis was due to a reaction in the nucleus ambiguous. No other cases of this sort have been reported in this country; however, the French have reported three such cases and the Germans one.

The latter cases of auditory and laryngeal involvement

are, like the hematuria case, very rare complications, but neuritis of the facial and peripheral nerves are not as uncommon. Kamman and Weisberg (79) record a case of polyneuritis and facial diplegia that followed a case of serum sickness, but recovered in 6 months. The authors state that usually this type of reaction is usually motor in nature, but may be sensory with twitchings and impairment of vesicle and rectal function. The polyneuritis generally begins in the lower extremities and gradually works upward, and eventually involves the facial nerve. Choked dises are noted in most of these cases; the cerebro spinal fluid shows an increased protein with a high lymphocyte count. Recovery usually takes place in 6 weeks to 2 years; however, there have been deaths recorded from respiratory failure. Kammon and Weisberg believe that the pathology in these cases is located in the dorsal root ganglia and peripheral nerves, and that the pathology consists of degeneration of the myelin sheaths with fragmentation of the axis cylinder, but there is no inflammation. The treatment recommended by these authors is pilocarpin sweats, potassium iodide by mouth, rest, and thiamine chloride sub-cutaneously.

Brachial plexus neuritis resulting from the use of anti-tetanic serum have been reported by Bubert (80), Hoagland (81), Brahdy (82), Ball (83), Lindemulder (84), Bennett (85), and Doyle (86). Bubert (80) records two cases in which only one case of the neuritis was preceded by serum sickness; both cases eventually fully recovered. Hoagland (81) reports one case that developed a serum sickness five

days after a 1500 unit prophylactic injection, the following day the patient developed a numbness and weakness in right deltoid. At the end of one year, this right deltoid (injection was given in left deltoid) was atrophic, and there was analgesia and hyperthesia. The author believes that the prognosis for this patient is poor in spite of the usual neuritis treatment that was given. Hoagland believes that the neuritis is caused by an edema of the nerves. Brahdy (82) records a case of brachial plexus neuritis that occurred in a patient after he had received two prophylactic injections of anti-toxin six months apart. In spite of the physio therapy that this patient received, twenty months after the attack of neuritis he still had a wrist hop and inability to extend his fingers. Because this patient was an alcoholic, Brahdy thinks it is possible that the alcohol fixed the serum in the nerves. The case recorded by Ball (83) developed one month after the injection; a serum sickness had developed one week after the injection. This patient was completely cured in three month's time with sinusoidal and galvanic current treatments. Lindemulder's (84) case of neuritis resulted in atrophy, probably permanent, in the deltoid and supraspinatus. Lindemulder believes that rest and abduction of arm at 90 degrees during the acute stage is the best treatment; hydro therapy and heat treatments should not be given until the acute stage has passed.

A. E. Bennett (85) reports and discusses five cases of neuritis resulting from horse serum; three of these cases completely

recovered, two only partially recovered. All five of these neuritis cases were preceded by serum sickness six to fourteen days after the injection of anti-tetanus serum (in one case 60 cc of anti-gas serum was given). All of the neuritis pains were located in the shoulder, and each case showed eventual atrophy of the shoulder muscles; particularly in supraspinatus, deltoid, and teres muscles.

In discussing this type of neuritis, Bennett indicates that the usual picture is that within a few hours after the onset of serum sickness severe neuritic pains develop. The pains usually involve the neck, shoulders, arms, and legs, and this pain is so severe that opiates are of little value. Flaceid paralysis then occurs within a few hours to a day or two, and this is followed by atrophy of the muscles. Muscle tenderness, hyperesthesia and dull pains persist for several weeks. The neurologic findings may consist of motor paralysis, atrophy, fibrillations, sensory loss, reduced or absent reflexes depending on what segments are involved.

As regards pathology, the suprascapular is the most frequent nerve involved, followed by axillary and long thoracic. All of these nerves originate from the 5-6-7 cervical nerves. To explain this localization, Bennett believes that the signs and symptoms are caused by vaso dilatation which results in edema of skin, muscles, bursae, and joint tissues; this edema produces compression on nerve trunks thereby producing a palsy in a few hours. It seems possible that this edema could occur in the intervertebral foramen,

boney grooves, or perineural sheaths of the nerves, thereby interfering with the blood supply to the nerves, causing an anoxemia with temporary or complete nerve cell and fiber death. Garcin and Bertrand (1935) proved by animal experimentation that repeated anaphylactic shock caused vaso-dilatations, perivascular infiltration, and at times minute hemorrhages with cellular destruction and marked meningeal reactions. Increased lymphocytosis has been observed frequently in the spinal fluid during the serum sickness stage; so possibly then a combination of a vascular disorder and edematous compression accounts for the neuropathologic picture of complete peripheral nerve palsy and muscular atrophy. The anterior horn motor neurons must be unaffected because complete regeneration usually occurs.

Immediate treatment during the serum sickness stage may prevent the neuritic complications. This treatment consists of intra-venous hypertonic sucrose to reduce the edema, artificial hyperpyrexia (103-104) also to reduce edema, also the use of epinephrine with pilo corpine and blanket sweat packs. The neuritis is treated by abduction splint at 90 degrees, general nutritive and vitamine therapy, and local heat. After the hyperesthetic stage physio-therapy and electrical stimulation are indicated.

Because this type of neuritis usually results because of a prophylactic injection of anti-toxin, the medico-legal aspects of such a case are very interesting, particularly to those clinicians associated with insurance companies that write compensation insurance.

In an attempt to gain facts concerning compensation, Bennett (85) sent a questionnaire to eighteen companies or compensation commissions. In replies from eleven companies, six stated they had no experience relative to complications from horse serum, two replied they had claims for this type of disability but no facts were given, one stated they had one serious case of this type, but the facts were unobtainable. The Traveler's Insurance Company replied that they had had two typical cases of brachial plexus neuritis resulting from horse serum; one case recovered in five months with compensation of over $500; the other case had not recovered since July 1937 and was still being carried on a 50% disability of the arm. Another company reported a case of right brachial neuritis with aphasia that resulted from horse serum; this patient was disabled for six months and received a total compensation of $2000. One of Bennett's cases that did not fully recover received compensation for one year, and a settlement on the basis of 50% disability of the arm. Consequently, one should not be careless in dealing out tetanus anti-toxin, and when anti-toxin is given the patient should be told of the beginning symptoms of serum sickness so treatment can immediately be started, thereby possibly preventing a disabling neuritis and incidentally save the patient a great deal of pain and the insurance companies money.

Doyle (86) in an excellent review of 47 cases of neuritis resulting from horse serum injections revealed the following facts:

1. Thirty-three out of the forty-seven cases were over 21 years of age.

2. In thirty-five cases the neuritic symptoms came on two days after the serum sickness developed.
3. The average length of the serum sickness was about 3 days.
4. Thirty-four out of 49 cases developed neuritis following injection of anti-tetanic serum.
5. The distribution of the neuritis in 49 cases.

(1) Superior brachial plexus - unilateral motor	13
(2) Mononeuritis (radial 7 - long thoracic 1)	8
(3) Optic neuritis	6
(4) Brachial plexus - bilateral motor	4
(5) Brachial plexus - bilateral sensorimotor	4
(6) Superior brachial plexus - unilateral sensorimotor	4
(7) Superior brachial plexus - bilateral motor	3
(8) Superior brachial plexus - bilateral sensorimotor	3
(9) Brachial plexus - unilateral motor	1
(10) Brachial plexus - unilateral sensorimotor	1
(11) C.N.S., meninges, brachial plexus - bilateral motor	1
(12) Urticarial edema of the brain and meninges	1

During the months from March (1941) through January (1942) 389 prophylactic injections of tetanus anti-toxin were given to 381 men who were constructing the Martin Bomber Plant at Fort Crook, Nebraska. Each injection consisted of 1500 units. The site of injection was in either the deltoid or the glutens; three injections were given in the rectus abdominus muscle. The majority of the prophylactic treatments were given for puncture wounds in the

hands and feet; in four cases of compound fractures a combination of gas and tetanus anti-toxin were given.

Every man received an intra-dermal skin test of either the anti-toxin itself or the plain horse serum. In this series twenty men showed a positive skin test; in nine of these men the are of erythema was over four centimeters and there was a definite wheal, and because their wound was thoroughly cauterized with phenol and ~~aponeal~~ OPENED no tetanus anti-toxin was given. In three of those that showed a positive skin test, the anti-toxin was given in one dose because the skin reaction did not show a positive before one-half to one hour after it was given. These latter three tests were done with tetanus anti-serum, one of the subjects developed a severe brachial plexus neuritis, the other two showed no reaction. In eight of the subjects that showed a positive skin test, the anti-toxin was given in 3-8 doses; none of these subjects reported any reaction.

In two instances a positive skin test was noted after a previous injection of 1500 units of anti-toxin. In six instances the skin did not test positive for horse serum after 1500 units had previously been given, and a second injection of 1500 units within a period of six weeks caused no reaction in these six men.

There was a total of fourteen cases of serum sickness, four of these cases gave a history of having had horse serum before. None of the fourteen cases of serum sickness showed immediate positive skin reactions to horse serum.

In one instance a serum sickness was followed by a brachial plexus neuritis. In three cases of serum sickness there resulted a questionable mild neuritis in the brachial plexus. I say questionable because in none of the latter three cases mentioned was there very severe pain, nor did the symptoms last more than four days.

Three hundred and thirty-seven injections were given on the day of the injury. Thirty-five were given one day after the injury, while a total of seventeen injections were given all the way from two to ten days after injury.

I believe it is of interest to note that seven men absolutely refused to take tetanus anti-toxin because of unpleasant reactions they had heard of; one man refused the anti-toxin because of a severe neuritis he had formerly developed in his leg from a previous dose of tetanus anti-toxin.

The majority of the serum sickness cases reported consisted of rash, malaise, axillary adenitis, fever, redness, swelling of the injection sight, and nausea and vomiting. In only one case was there a severe urticaria. All of these cases developed 7-10 days after the injection, and all were given epinephrine (.3-1 cc) which afforded immediate but temporary relief. Histaminase was given in only four cases of serum sickness, and in only one case were any favorable results seen. In cases that had a slight rash, luke warm starch baths were recommended which gave relief from the pruritis, hot packs were applied to the injection site. None of the cases of serum sickness lasted more than four days.

Because of the rarity of a true brachial plexus neuritis from horse serum, I believe that my one case of such a condition would be of interest.

Case history: On June 25, 1941, patient stepped on a nail; he immediately reported to the hospital where he was given 1500 units of tetanus anti-toxin, and the wound was opened and cauterized with phenol. The anti-toxin was given in the gluteal region. The skin test done at this time with the anti-toxin was negative. Ten days later on July 3, patient stated that he noted severe "cramps" in right shoulder region. These cramping pains soon spread over to the left shoulder. The next day, the patient went to his own doctor who told him he had neuritis. At this time the patient complained of numbness and tingling in the tips of the 3-4-5 fingers of left hand; the right arm at this time was relatively free from any pain. This patient was treated by his own physician with thiamine chloride, local heat applications, and diathermy. By the eleventh of July the patient was unable to abduct his ~~right~~ LEFT arm because of severe pain; there was no evidence of paralysis at this time. The treatment mentioned above was continued and by July 21, the patient was able to return to work; at this time he had about 80% function of his ~~right~~ LEFT arm. Re-examination of the patient on September 5 showed that there was a definite muscle atrophy over the ~~right~~ LEFT scapula; the patient complained that his ~~right~~ LEFT arm was weaker than the ~~left~~ RIGHT, and examination proved this to be true.

It is of great interest to note that this patient's neuritis was not preceded by a severe serum sickness; although he states that the day following the injection the site of the injection was red and swollen; also he complained of a slight headache and malaise at that time.

Certainly from the evidence gathered by reviewing these 389 cases no startling conclusions can be reached; however, first and foremost, it is important to note that there were no cases of tetanus among the 5000 men who were working on construction of the Martin Bomber Plant at Fort Crook, which, after all, is the desired result from tetanus prophylaxis.

Conclusions:

1. Skin testing done with pure horse serum gives more prompt and more clear-cut reactions.

2. A negative skin test does not rule out the possibility of serum sickness.

3. Serum sickness and neuritis are not common enough to prohibit the use of horse serum anti-toxin.

4. One injection of horse serum does not always sensitize a person to horse serum.

5. The usual case of serum sickness occurs about 7 days after prophylactic treatment, and lasts only about four days.

6. Epinephrine and warm starch baths are beneficial in alleviating the symptoms of serum sickness.

7. An insufficient number of cases were treated with histamine to warrant any definite conclusions.

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ADDENDA

18. Suvansa, Quoted from Reverence 17.

24. Dowles, H. G., Serum Treatment For Tetanus; Brit. M. J.,1: 809, April 17, 1937.