can be taken. Two might be mentioned. One is that the globulin solution contains nothing but antitoxic globulins. We do not know what antitoxin is, but we believe that the globulin solution still contains much non-antitoxic substance, and we certainly hope to remove still more of the non-antitoxic globulins. The other is the claim that the special precipitating agent used gives a different final result. It seems to me that it is very creditable to the honesty and intelligence of the producers that they are so fair and sensible in their claims for their special preparations.

315 West Seventy-sixth Street.

THE COMMERCIAL PREPARATIONS OF TETANUS ANTITOXIN *

JOHN F. ANDERSON, M.D.

Passed Assistant Surgeon and Assistant Director Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service

WASHINGTON, D. C.

Antitetanic serum is the serum of certain animals, usually that of horses, immunized to the toxins of the tetanus bacillus. It is marketed in both the liquid and dry forms. Some manufacturers prepare an antitetanic

by Behring (2), the French method of Roux, and (3) the Italian method after Tizzoni.

The European methods are admitted, even by their users, to be unsatisfactory and, in the main, not accurate; in addition, they are complicated and difficult to use. The American unit commends itself for its simplicity, directness, and accuracy. I am informed that it may be adopted officially by the Belgian government.

There is at the present time no standard for serums for veterinary use. We examined, in the Hygienic Laboratory, several different makes of veterinary tetanus antitoxin and found most of them to contain less than 25 units per cubic centimeter, while the minimum strength of the serums for human use now on the market—over which there is federal control—is at least 150 units per cubic centimeter, and much of it considerably stronger.

The need of uniformity in measuring the strength of tetanus antitoxin has long been felt and is very evident from the accompanying table,² from which it will be seen that before the promulgation of the American standard the tetanus antitoxin on the market varied extravagantly in the unit strength claimed.

As will be seen from the table, most of the foreign serums were far below the American in potency.

TABLE SHOWING THE DIFFERENCES IN THE METHODS OF TESTING TETANUS ANTITOXIN BEFORE THE ADOPTION OF
THE AMERICAN UNIT

Name of Manufacturer.	Labeled.	Contents c.c.	Units claimed according to special methods of standardiza- tion, per c.c.	Units accord- ing to the American standard, per c.c.
New York department of health, Albany (submitted by Dr. H. D. Pease for comparison).....	One immunizing dose (No. 2929 F.)		0.5	434
New York City department of health (submitted by Dr. W. H. Park for comparison).....	1,000,000 immunizing units (No. 2121).	..	700	166
H. K. Mulford Co. (bought on open market).....	Tetanus Antitoxin, 5 fach. Normal, Prüfungs dose=1/500. *	10	100,000	77
Farbenfabrik vorm. Meister Lucius & Bruning, Hoechst, a/M (submitted for comparative tests).	60,000,000 units.	10	6,000,000	333
H. K. Mulford Co. (No. 9971 submitted for tests).		..	60,000	90
Parke, Davis & Co.		..		700
New York department of health, Albany (submitted by Dr. H. D. Pease for comparison).....		..	75	769
Pasteur Institute, Paris (10 c.c. fluid).....	[Unit value not stated.]	10	Not stated.	40
Pasteur Institute, Paris.	[Unit value not stated.]	10	Not stated.	40
Tizzoni (No. 2912, Dry).....	[Unit value not stated.]	10	Not stated.	83.3†
Pasteur Institute (No. II, 7).....	[Unit value not stated.]	10	Not stated.	66
Institut Bactériologique de Lyon et du Sud-Est...	[Unit value not stated.]	10	Not stated	‡

* Dissolved in 26 c.c.

† This equals 833 units per gram of the dry serum.

‡ Less than 50.

globulin; this contains a solution of the globulins of the blood, which are soluble in sodium chlorid solution, together with the antitoxin.

All tetanus antitoxin sold in interstate commerce in the United States must conform to the official standard adopted by the United States Public Health and Marine-Hospital Service, which was officially promulgated Oct. 25, 1907.¹ This unit may be defined as follows: "The immunity unit for measuring the strength of tetanus antitoxin shall be ten times the least quantity of antitetanic serum necessary to save the life of a 350-gram guinea-pig for ninety-six hours against the official test dose of a standard toxin furnished by the Hygienic Laboratory of the United States Public Health and Marine Hospital Service."

Besides the American unit above alluded to, there are three other units for measuring the strength of tetanus antitoxin. They are (1) the German method described

Tetanus antitoxin is used both as a prophylactic and as a curative agent in tetanus. The dried and powdered serum has been used as a dusting-powder for wounds. Used as a prophylactic, the dose is 1,500 units; as a curative it should be given in doses of 3,000 to 20,000 units, repeated during the course of the illness.

Tetanus antitoxin is made in the following laboratories: Parke, Davis & Co., Detroit, Mich. (license No. 1); H. K. Mulford Co., Philadelphia, Pa. (license No. 2); Lederle Antitoxin Laboratories, New York, N. Y. (license No. 17); New York State Department of Health, Albany, N. Y., and the Department of Health, city of New York.

The liquid serum is marketed either in syringes ready for use or in glass vials. Each syringe of tetanus antitoxin made by the American producers contains from 1,500 to 5,000 units without regard to the volume of the serum; the unit value per cubic centimeter varies from 150 to 500 or 600 units.

Many of the foreign serums, as is the case with most of the foreign diphtheria antitoxins, are labeled to con-

* Read in the Section on Pharmacology and Therapeutics of the American Medical Association, at the Sixtieth Annual Session, held at Atlantic City, June, 1909.

1. Rosenau, M. J., and Anderson, John F.: The Standardization of Tetanus Antitoxin (an American Unit Established under Authority of the Act of July 1, 1902), Bull. 43, Hyg. Lab., U. S. P. H. and M.-H. S., Washington, 1908.

2. Bull. 43, Hyg. Lab., U. S. P. H. and M.-H. S., p. 11.

tain so many cubic centimeters and do not give the number of units in the package or per cubic centimeter, and are almost uniformly weaker in antitoxic strength than the serums produced in the United States.

The affinity of the nerves for the toxin and its subsequent binding by them explains why tetanus antitoxin is often of so little value after the symptoms have developed. The antitoxin can, however, neutralize any new toxin that may be formed in cases in which the focus has not been removed and should, for this reason, invariably be used in all cases of tetanus.

Tetanus antitoxin at the present time is in the Belgian, French, and Swiss pharmacopeias. Both the dry and the liquid preparations are recognized by the French Pharmacopeia.

As diphtheria antitoxin is in the United States Pharmacopeia, and as there is now an American standard for determining the strength of tetanus antitoxin, this product should by all means be included in the next revision of the United States Pharmacopeia. Its great value as a prophylactic alone entitles it to admission without regard to its value in the treatment of developed tetanus. I should like to see this Section pass a resolution favoring its admission to the Pharmacopeia.

It may not be amiss to add a few words in regard to the federal control of therapeutic serums, especially of tetanus antitoxin.

Before the adoption of the American unit for tetanus antitoxin by the United States Public Health and Marine-Hospital Service there were as many different units or standards as there were producers of tetanus antitoxin. The physician, in using this serum, could have no idea of the number of antitoxic units the serum contained, as one maker's product was labeled "to contain 6,000,000 units per c.c." and another, probably just as potent, 0.75 per c.c., when in truth, according to the official standard, the first had only 90 units per c.c. and the latter about 770 units per c.c..

The great good that has come from the federal control of therapeutic serums may be summarized as follows:

1. The physician can be assured that every package of tetanus antitoxin now contains at least the number of units claimed.
2. All serums are now examined for, and are required to be free from, bacterial or toxic contamination.
3. The amount of preservative contained in the serums is not excessive.
4. There has been a progressive increase in the potency of tetanus antitoxin without a corresponding increase in cost.
5. A uniform standard having been established, definite amounts of tetanus antitoxin can be used so that data will gradually be collected as to the amount of serum necessary to be used for immunizing and curative purposes.

ABSTRACT OF DISCUSSION

DR. W. H. HUTCHINGS, Detroit: I feel that the valuable work of Dr. Anderson and Dr. Rosenau in formulating this standard unit of tetanus antitoxin should not pass here without some commendation. We have now for the first time definite knowledge of how much antitoxin we are using. Previously we measured the amount given in cubic centimeters with no knowledge—except the word of the manufacturer—of how strong it really was. The value of such information will be appreciated when we see that the serum of one manufacturer, who claimed 6,000,000 units per c.c., contained according to the present standard, only 90; while another

serum, which was stated to contain 0.75 of a unit, in reality, contained 769. As the result of the adoption of this standard we can now use the serum of any American manufacturer and know just how much we are giving. I would suggest that in future reports of our cases we state the number of units employed rather than the number of cubic centimeters. In this way we will soon have valuable data for comparison.

A large majority of manufacturers use either phenol or tricresol for preservation in various serums. The amount is usually 0.04 per cent. Consequently every time we give 10 c.c. of antitetanic serum we give at the same time a curative dose of phenol as recommended by Baccelli. Possibly some at least of the reported cures of developed tetanus are due more to the carbolic acid than to the serum.

DR. E. R. LARNED, Detroit: If Dr. Anderson said that the antitetanic unit represented ten times the amount of serum necessary to neutralize the killing dose of tetanus toxin when injected into a guinea-pig of standard weight, 350 grams, then I have misunderstood the technical definition of antitetanic unit and antidiphtheric unit. My conception is that the antidiphtheric unit represents one hundred times the amount of serum necessary to save the life of a guinea-pig of standard weight (250 grams), when injected into the pig, together with minimum lethal dose of diphtheria toxin; that an antitetanic unit represents one thousand times the amount of serum required to save the life of a guinea-pig, of standard weight (350 grams), when injected at the same time with the M. L. D., of tetanus toxin. I understand that the government authorities have required that the standard dose of tetanus toxin to be administered to pigs in standardizing the serum into units is ten times the M. L. D., of toxin and that one hundred times the amount of serum necessary to neutralize the standard test dose of toxin (ten times the M. L. D.), of the same toxin represents the unit; or in other words, the antitetanic unit is one thousand times the amount of antitetanic serum required to save the life of a guinea-pig of standard weight (350 grams) when the serum and the toxin are injected at the same time.

One point that I think served to cloud the solution of the question of antitetanic serum's efficacy in the hands of the every-day practitioner, is the fact that the ordinary practicing physician knows nothing whatever about the necessity of the very early and frequent administration of sufficient quantities of the serum. My experience, which has been large in this particular regard, shows me that physicians are condemning antitetanic serum as a curative agent, because they wait too long, use too small quantities, and give up too quickly. A coal miner in Springfield, Ill., who had received an accidental gunshot wound, developed tetanus, his condition was pronounced hopeless and he was given up by the attending physician. Under the total administration of 198,000 units of serum, he recovered. The opinion in general seems to be that antitetanic serum is of no value for curative purposes. Professor Ehrlich has told me that antitetanic serum, in his opinion, was just as specific for tetanus as antidiphtheric serum for diphtheria, provided it was used early and often enough and in sufficiently large quantities.

DR. W. H. PARK, New York City: During the past few years, and especially the last year, we have found in New York that, when a large intravenous dose is given within a few hours of the onset of the symptoms, the effect is marked. More than 50 per cent. of the patients I have seen thus treated have recovered, some of whom I feel perfectly sure would have died without the serum. Ordinarily the surgeon waits a number of hours to make up his mind and then sends for the serum. He then frequently waits several hours longer until it arrives. At the first sign of actual tetanus an intravenous injection of ten to twenty thousand units should be given, to be followed every twelve hours by further injections. If this is done, we will certainly see some good results. The later injections can be given subcutaneously if there is difficulty in giving it intravenously.

DR. JOSEPH MCFARLAND, Philadelphia: How we are to arrive at the correct dosage of tetanus antitoxin I am unable to imagine. I would like to say a word about some observations made on tetanus in thirty-five horses. Sometimes a horse shows symptoms of tetanus, slowly increasing, and

after a prolonged period recovers without any treatment at all. At other times, the horse develops symptoms, becomes rapidly worse, and dies in a few days. In the former cases recovery takes place without antitoxin treatment, in the latter, doses of antitoxic serum up to a liter at a time produce no improvement.

DR. W. H. HUTCHINGS, Detroit: In connection with a comparative experimental study of the various methods of treating tetanus, I have been conducting a series of experiments to determine the curative value of serum when used alone. For this purpose, I have used sheep with long tails. A splinter of wood infected with toxin-free spores was placed in a pocket at the tip of the tail. With the first appearance of symptoms of tetanus, six to seven days later, the tails were amputated 20 centimeters above the point of inoculation. At this time 2 c.c. of blood from the jugular vein of the infected sheep contained enough toxin to kill a 350 gram guinea-pig when injected subcutaneously. Then 4,500 units of antitetanic serum were injected intravenously as mentioned by Dr. Park. Twenty-four hours later, 2 c.c. of this sheep's blood did not contain a trace of toxin. Nevertheless, despite the daily injection of 4,500 units of serum all but one of the sheep died of tetanus. The symptoms were not influenced to the slightest degree by the serum. This experimental evidence goes to confirm the belief of many authors, based on clinical observations, that after the symptoms of tetanus have become manifest, antitetanic serum is valueless as a curative agent, no matter whether it is used subcutaneously, intravenously, intraspinally or intraneurally. Antitoxin will neutralize the toxin present in the body which has not combined with the nerve cells, but it will not break up this combination, the results of which kill most of our patients.

DR. J. F. ANDERSON, Washington, D. C.: The tetanus unit may be defined as ten times the least quantity of antitetanic serum necessary to protect the life of a 350 gram guinea-pig against the test dose of a standard toxin furnished by the Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service.

I think the pathology of the disease shows us how futile is the use of tetanus antitoxin after the symptoms have fully developed. The toxin, being bound by the nerve substance, cannot be reached by the antitoxin in the circulation, though the latter of course can neutralize any new toxin that may be formed if the original focus of infection has not been removed. I think it should be used, however, in all cases of developed tetanus, for frequently the surgical procedure has not been thorough.

I think Dr. Park's point that the serum should be administered intravenously is well taken and exceedingly important. We know that when a dose of antitoxin is given subcutaneously the maximum absorption is not attained till twenty-four to forty-eight hours after the injection, and much valuable time would be lost if the serum were not administered intravenously.

DR. JOSEPH MCFARLAND, Philadelphia: The large doses to which I referred were given subcutaneously, not intravenously.

VACCINE THERAPY: GENERAL PRINCIPLES *

MARK W. RICHARDSON, M.D.

BOSTON

In studying the question of specific therapeutics it is important to bear in mind, in the first place, the fundamental distinction between passive and active immunity. In the utilization of passive immunity in the cure of disease, aid to the individual comes from without. Moreover, the mediation of a second animal is required, and the protection given is fleeting, though its immediate power may be great. By the inoculation of lower animals with animal or vegetable cells or their toxins, a

large variety of immune serums has been produced. While most of these have been found to be highly potent in protection against infection, especially in animal experiment, their curative power in the presence of declared disease has been distinctly limited. Diphtheria still stands out as the one disease in which passive immunity has proved its worth emphatically, though results almost as remarkable have been seen recently in serum treatment of cerebrospinal meningitis. Less degrees of success have been noted in dysentery, cholera, typhoid fever, tetanus, snake-poisoning and other infections and intoxications.

In the use of vaccines, on the other hand, we aim at the production of an active immunity. We do not bring to the sick individual immune substances already manufactured; we endeavor to stimulate him to produce for himself a larger amount of these immune substances. To do this we introduce into his body more morbid material in order that he may, by manufacturing an increased amount of the protective bodies, inhibit the growth of the invading organisms and cut short his disease.

Success in this method of treatment presupposes that the patient is not already completely overwhelmed with poison. He must respond to the added stimulation. Furthermore, if this procedure is to bring about, as it should, increased bacterial destruction with the setting free thereby of an increased amount of endotoxin, this destruction must not be too rapid or excessive, lest efforts to cure do harm through hyperintoxication.

Bacterial immunity is brought about through the action of a great variety of different, though related, immune substances, and as a result of inoculation with vaccines there may be formed antitoxins, antiendotoxins, lysins, agglutinins, precipitins, opsonins, and other allied products, the relative importance and proportion of each varying in different infections.

By bacterial vaccine is generally meant a culture of the special organism sterilized by heat, or otherwise, and suspended in known proportions in normal salt solution.

Living organisms, attenuated either in number or virulence, have been used in a few instances. Theoretical considerations would indicate that the use of living bacteria would be followed by results more favorable than those seen after inoculation of the dead organisms, but it is manifest that such use would be in many instances accompanied by great danger. The greater efficiency of living organisms, however, should be constantly borne in mind, in order that, in the process of sterilization, the bacteria may be changed in their characteristics as little as possible.

In this connection may be mentioned the work of Strong, in the Philippines, who found that by the inoculation of plague bacilli of attenuated virulence, he could produce in human beings a much stronger immunity than that ever produced by dead bacilli. Furthermore, in one instance at least, living typhoid bacilli have been used by Italian observers in the treatment of typhoid fever, with what are said to have been excellent results. Finally, living bacilli have been used by Webb, Williams, and Barber¹ in the treatment of tuberculosis. In this treatment the bacilli are so diluted in number that inoculations are begun with a single bacillus, the dose being gradually increased thereafter.

As a general principle, it is better, if possible, to use autogenous vaccines. At any rate, if good results are

* Read in the Section on Pharmacology and Therapeutics of the American Medical Association, at the Sixtieth Annual Session, held at Atlantic City, June, 1909.

¹ Webb, Williams and Barber: Jour. Med. Research, January, 1909.