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Address

SOME NEGLECTED FACTS IN THE BIOLOGY OF THE TETANUS BACILLUS.

THEIR BEARING ON THE SAFETY OF THE SO-CALLED BIO-
LOGIC PRODUCTS.*

THEOBALD SMITH, M.D.

George Fabyan Professor of Comparative Pathology in the Harvard
University Medical School; Director of the Antitoxin and
Vaccine Laboratory of the Massachusetts State
Board of Health.
BOSTON.

Medical science, like any other applied science, deals not so much with abstract biologic principles, as with the facts of every day life, illumined and made orderly by these principles. Through a knowledge of such principles the facts of our concrete existence may often be controlled and rearranged for our good. Like other applied sciences, medical science often uses incomplete truths, data with gaps in them, methods inadequately tested or not sufficiently developed. Hence the accidents of our daily life. Measures designed to do good may have concealed within them incidental dangers due to faulty processes. It is one of these to which I wish to call your attention this evening. It involves the principle of *non nocere*, one which we must ever keep before us in the prevention and treatment of disease.

About nine years ago, in a very brief article,¹ I called attention to the inefficiency of discontinuous boiling or steaming when large quantities of bouillon are to be sterilized in relatively shallow layers. In the routine preparation of diphtheria toxin it was found that the spores of anaërobic bacteria frequently survived the repeated steamings. After the diphtheria bacilli had established anaërobic conditions by forming a surface pellicle or membrane, these spores began to germinate, and more or less multiplication took place. It was a routine practice of the laboratory to submit all such cultures to microscopic examination and titration. One or both methods would reveal any accidental contamination.

The anaërobic encountered in these contaminated flasks were reserved for future study by removing the diphtheria bacilli by boiling from a small portion of the culture fluid, and a considerable number of cultures were collected, only a few of which have survived the accidents of time. One of these cultures was pathogenic, for guinea-pigs died over night after a subcutaneous injection of one cubic centimeter of a bouillon culture. There were no lesions, local or general, beyond an occasional trace of edema at the point of inoculation, and marked congestion of the lungs.

Nothing more was done until the past summer, when I

began a more serious study of the anaërobic in my collection. The nature of this culture was not recognized until minute doses were employed. The disease then showed a longer period of incubation, and, to my surprise, the animals (rabbit, pigeon, guinea-pig, white rat) became affected with tetanus. A more thorough microscopic study of the culture, from day to day, revealed the presence of an anaërobe, beginning spore formation within 24 hours, and masking the presence of a second anaërobe which produced spores after the second or third day, and which had all the morphologic characteristics of the tetanus bacillus. That the spores of the tetanus bacillus should survive three steamings, of 20 minutes each, was new to me, and I at once began to test the resistance of the spores and to examine the literature on this point.

Kitasato,² well known as the first who isolated the tetanus bacillus in pure culture and studied its biologic characters, stated that the spores resist moist heat at 80 C. for one hour, but that they are killed in streaming steam in 5 minutes. Vaillard and Vincent,³ closely following Kitasato, stated that the spores, heated in the presence of moisture in a closed vessel, would resist destruction at 80 C. for 6 hours; at 90 C. for 2 hours; at 100 C., 3 to 4 minutes; that they were not always destroyed in 5 minutes, but never resisted more than 8 minutes at 100 C. These statements by Kitasato and by Vaillard and Vincent found their way into textbooks, some authors quoting the former, others the latter. In the volume of Kolle and Wassermann's large hand-book containing Lingelsheim's article on tetanus and bearing the date of 1903, Kitasato's original statement is quoted without comment or dissent.

The extended use of gelatin as a hemostatic in dangerous and otherwise uncontrollable hemorrhages, which led to a series of fatal cases of tetanus in the years 1901 to 1903, called attention to the resistance of tetanus spores to the temperature of boiling water. Levy and Bruns,⁴ taking these unfortunate accidents as a text, determined anew the resistance of tetanus spores. According to them, destruction begins at 8½ minutes at 100 C.; after 15 minutes very few survive; after 30 minutes none.

In a short bulletin, Anderson⁵ calls attention to the presence of tetanus spores in commercial gelatin, as determined by Levy and Bruns. A tetanus bacillus isolated by him from one of seven samples of gelatin was killed between 20 and 30 seconds at 100 C.

Tuck⁶ next takes up the same subject in view of the dangers of the subcutaneous injection of gelatin. Tetanus cultures, pure or mixed with *B. subtilis*, were always

* Read, Dec. 18, 1907, at a joint meeting of the Chicago Pathological Society and the Chicago Medical Society.
1. Jour. Exper. Med., 1898, iii, p. 647.

2. Zeitschr. f. Hyg., vii, p. 225.

3. Annal. de l'Institut Pasteur, 1891, v, p. 1.

4. Grenzgeb. d. Med. u. Chir., 1902, x, p. 235.

5. U. S. P. H. and M.-H. Service, Hygienic Laboratory, Bull. No. 9, September, 1902.

6. Jour. Pathol. and Bact., 1903-4, ix, p. 38.

killed after 10 minutes' boiling. Some samples of gelatin, accidentally containing tetanus spores, were not sterilized after three boilings, of 30 minutes each, on consecutive days. Tuck does not state, however, that the spore-bearing anaërobes other than tetanus were responsible for this resistance. His concluding statement would lead us to think that they were, for, to allay unnecessary alarm concerning the use of gelatin, he says: ". . . I am fully convinced that no spores of tetanus can resist boiling for over 20 minutes."

Falcioni⁷ is the last observer dealing with the same theme. He impregnated gelatin with spores of tetanus bacilli grown in agar or broth for 10 to 12 days, and used Koch's steam sterilizer. The gelatin was exposed in 2, 5 and 10 per cent. solutions. He found the spores to resist destruction for 2½, but not for 3 hours, in streaming steam.

The foregoing results are sufficiently varied and conflicting to suggest to us, on first thought, that races of tetanus bacilli exist, the spores of which vary widely in their resistance to moist heat at 100 C. Before resting, however, on this inference, it would be necessary to know the tendency to spore formation in different media and at different temperatures; the age of the culture at which spores are ripe, and, therefore, most resistant; the reaction of the medium in which the spores are boiled or steamed, because all of these variable factors have probably entered into the experiments quoted.⁸

Before I had informed myself of the work done thus far I had made some experiments to determine the resistance to boiling of two cultures in my hands—one obtained from presumably sterilized bouillon (Culture 4);⁹ the other brought by me, in 1896, from a large German institute (Culture 3).

The method employed to produce a rich crop of spores is one which I have used for many years and to which attention has been called in several short papers.¹⁰ To ordinary bouillon, in suitably constructed fermentation tubes, is added a bit of kidney, or spleen or liver from a rabbit or guinea-pig, just killed with chloroform. The piece of tissue is torn or pinched away from the organ with fine sterile forceps and varies from ½ to ¾ cm. in bulk. This is pushed well into the connecting tube, where it remains. The tubes need not be freshly prepared. They respond by growth even after standing for weeks in the laboratory. Sugar should not be added.

Animals which are to yield the tissues should be perfectly well. There should be no ulcers or other sores on them. They should not have been inoculated with bacteria of any kind for at least a month previous. They

should be handled with great gentleness and not chloroformed in such a way as to cause them to struggle. The reason for these precautions is that any lesion or previous inoculation of bacteria may lead to the distribution and prolonged latency of such bacteria in the body and these are brought to light by the large pieces of tissue used in the culture medium which is very sensitive to both aerobic and anaërobic bacteria. The struggling of the animal and rough handling may lead to slight injuries through which bacteria may enter the circulation. In spite of all these precautions fermentation tubes prepared in this way occasionally become clouded. Hence, they should only be used after an incubation of three or four days. Usually a slight clouding of the fluid in the open branch of the tube in which a bit of liver has been placed is due to a fine granular precipitate. Such clouded fluid should, however, be examined carefully microscopically.¹¹

When tubes prepared in this way are inoculated with material containing spores or bacilli a rapid and abundant multiplication takes place. The spore production is especially rich in and about the piece of tissue. Fluid from such cultures was used to determine the resistance of the spores at the temperature of boiling water or streaming steam.

TETANUS 3.

EXPERIMENT 1.—Culture in a fermentation tube, as above described, nine days old. Five c.c. of turbid fluid placed in thick-walled test tubes and the latter tightly stoppered with rubber stoppers, each perforated with a glass tube drawn out into a capillary, free extremity. Tubes were completely immersed in boiling water, except the capillary vent through which the air and steam could freely enter and escape. After the exposure for given periods of time, about 1 c.c. of the boiled fluid was added to fermentation tubes to determine the presence or absence of living spores. The culture fluid exposed to boiling water for 10, 20 and 40 minutes contained living spores, as proved by the successful subcultures. Fluid boiled 60 and 80 minutes failed to produce growth in subcultures.

EXPERIMENT 2.—Culture nine days old. Tubes about 6 mm. in diameter, drawn out and sealed at both ends in the flame, and containing about 1 c.c. culture fluid and an equal volume of air, were exposed to streaming steam in the Arnold sterilizer for 20, 40, 50, 60 and 70 minutes. The tubes were then opened and the entire contents of each allowed to flow into a fermentation tube. All cultures, except the one receiving the contents of the 60-minute tube, developed and contained only tetanus bacilli.

EXPERIMENT 3.—Culture in fermentation tube containing fermented bouillon, plus tissue from a guinea-pig. In incubator sixteen days. Total age, eighteen days. Spore-bearing bacilli very abundant, as usual. Only a few free spores seen. The arrangement for exposure of the culture fluid was the same as in Experiment 1, save that a large boiler, with a tight-fitting cover was used. The test tubes were completely immersed in the boiling water. Tubes were exposed 60, 90 and 120 minutes. To the last-named enough gelatin was added to make a 5 per cent. solution. This was done to determine if gelatin increased the resistance of spores, as suggested by Falcioni's⁷ results. All the subcultures, to each of which from 2 to 3 c.c. of the exposed culture had been added, remained sterile.

TETANUS 4.

EXPERIMENT 4.—Culture six days old. Portions exposed in test tubes to boiling water, as described under Experiment 1, for 10, 20 and 40 minutes. All subcultures positive.

EXPERIMENT 5.—Culture eight days old. Tubes exposed as in preceding experiment, at 60, 80 and 100 minutes. Subcultures of fluids heated 80 and 100 minutes remained clear.

11. This method of using tissues to stimulate the growth of anaërobes has recently been rediscovered by Tarozzi (Centr. f. Bakt., Orig., 1905, xxxiv, p. 619).

7. *Annali d'igiene sperimentale*, 1904, N. S., xiv, p. 319.

8. In the case of nutrient gelatin, which has been a favorite medium, I find sporulation very feeble and involution forms common. It is quite probable that such cultures would resist boiling but feebly. The use of dextrose in fairly large amounts, such as 1 or 2 per cent., has been frequent among bacteriologists, although this amount is inimical to rapid spore formation.

9. A pure culture was obtained from the mixed culture on blood-agar in desiccating jars, according to Bordet. Quite unexpectedly, pure cultures were also obtained with bits of liver from a white rat inoculated subcutaneously in the thigh with the impure culture. As a rule, and in harmony with the results of earlier observers, tubes inoculated with large bits of organs, and with ¼-½ c.c. of heart's blood of rabbits and guinea-pigs inoculated with tetanus bacilli remained sterile. The colonies of tetanus bacilli spread very rapidly on blood-agar plates and the hemolytic area produced by a single colony may reach one centimeter in diameter. This tendency to spread made it difficult to obtain pure cultures from the colonies of the contaminating anaërobe whose colonies were very compact, for the tetanus colonies invaded them, though this invasion was not recognizable under low powers. I succeeded more quickly in obtaining pure cultures of this latter organism by boiling the mixed culture for 85 minutes. This destroyed the tetanus spores, but not those of the associated species.

10. *Jour. Boston Soc. Med. Sci.*, 1899, p. 340; *Jour. Med. Res.*, 1905, xiv, p. 193.

That the spores surviving prolonged boiling belonged to the true tetanus bacillus was demonstrated by testing the subculture of the 60-minute tube of this experiment on two guinea-pigs. Both guinea-pigs acquired tetanus after the subcutaneous injection of .00075 c.c. and 00005 c.c., respectively.

EXPERIMENT 6.—Made at the same time and in the same manner as Experiment 2. Culture nine days old. Contained also an oval-spored anaërobic bacillus. Placed in sealed pipettes, and exposed to streaming steam for 20, 40, 50, 60 and 70 minutes. Subcultures from all, excepting the 70-minute tube, contained tetanus bacilli. The subculture of the 70-minute tube contained only the oval-spored bacillus.

EXPERIMENT 7.—Performed at the same time and in the same way as Experiment 3. Culture fifteen days in thermostat. Total age seventeen days. Spore-bearing bacteria very abundant. Tubes exposed in boiling water with those of Experiment 3 for 60, 90 and 120 minutes. A tube containing culture fluid plus 5 per cent. gelatin was exposed 120 minutes with the rest. The subcultures of these four tubes remained sterile.

EXPERIMENT 8.—This experiment was to determine whether any spores would survive steaming for 20 minutes on three consecutive days. To imitate the usual laboratory environment as closely as possible, the following tubes were prepared with tetanus cultures, nine days in the thermostat, and containing spore-bearing bacilli:

BACILLUS 4.

A: Ordinary test tube, 1 inch in diameter, plugged with cotton wool, into which about 8 c.c. culture fluid was put with pipette.

B: The same kind of tube, into which 5 c.c. culture fluid, plus 7 c.c. freshly boiled bouillon was put.

C: Ordinary $\frac{5}{8}$ inch test tube, plugged with cotton wool, containing 2 c.c. culture fluid, plus 10 c.c. fresh bouillon, making a column 9 cm. high.

BACILLUS 3.

D: Ordinary test tube, 1 inch in diameter, containing about 6 c.c. culture fluid, and 6 c.c. freshly boiled bouillon.

This arrangement was designed to favor germination of the spores between the steamings in B, C and D. In A, the absence of freshly boiled bouillon would tend to leave the spores unchanged. There is, of course, nothing to show that tetanus spores were actually stimulated to germinate under the given conditions. An Arnold sterilizer was used and the tubes kept at 70 F. in the intervals. The following table gives the amount of fluid added to fresh fermentation tubes after each steaming, and the result indicated with the sign +, when multiplication took place.

Designation of culture.	Amount transferred to fresh fermentation tubes after:		
	1st steaming.	2d steaming.	3d steaming.
4. A.	1 c.c. +	1 c.c. —	6 c.c. —
B.	1 c.c. +	2 c.c. —	9 c.c. —
C.	2 c.c. —	3 c.c. —	7 c.c. —
3. D.	1 c.c. +	2 c.c. +	9 c.c. +

In this test the spores of Bacillus 3 were distinctly more resistant than those of 4. Spores in all but the dilution C survived the first steaming. None but Culture 3 survived the second and third. It should be noted here that the tubes were actually exposed 20 minutes each time. The reckoning began only after the thermometer of the steam chamber had registered a constant temperature.¹²

The foregoing experiments, though merely tentative and suggestive of more detailed and thorough investigation of the tetanus spore, are sufficient to prove that under the conditions of cultivation, as described above, some spores survive a single boiling or steaming for

20 minutes regularly, usually for 40 minutes, and occasionally for 60 minutes. In one case 70 minutes' exposure did not destroy all spores. They are sufficient to prove the possibility of tetanus spores appearing in culture fluids sterilized by discontinuous boiling or steaming in routine laboratory work, even when a relatively small amount of fluid is exposed to streaming steam for fully 20 minutes on three successive days.

There is also evidence to show that after 40 minutes' exposure a large portion of spores are killed, for the tubes of bouillon inoculated with them usually become clouded after 36 hours. Cultures of spores exposed 20 minutes became clouded within 24 hours. That there are spores which resist steaming for 21½ hours, as claimed by Falcioni,⁷ needs further confirmation in view of the facts given above.

There is to-day a widespread tendency to accept and apply the principles of immunity or specific resistance toward parasitic invaders in the routine treatment of certain infectious diseases, and in the prevention of such diseases as well. To what extent the application of methods of immunization may grow will depend, to a great degree, on the special education of the masses in the true nature of disease, and their willingness to undergo treatment as a preventive measure. Moving parallel with this application of the principles of immunity and depending on it is the growth in the use of so-called biologic products in the prevention and treatment of disease.

These may roughly be defined as obtained directly or indirectly from the animal body. Leaving aside those products which are derived from the animal body by chemical processes and designed for administration by the mouth, I wish to confine my remarks to those with which the body is inoculated, or which are injected into it. Twenty years ago animal vaccine was the chief, if not the sole product, used in this way. Then came the antitoxic and bactericidal sera, chiefly derived from the horse. To-day we have various bacterial products grown chiefly in bouillon or in media made with it as the chief basis. The subcutaneous application of gelatin as a hemostatic has already been mentioned.

Groups of cases of tetanus have been associated at some time in the recent past with vaccine, antitoxic sera, gelatin and bacterial vaccines. The occurrence of occasional stray spores in vaccine was demonstrated by Carini.¹³ Such vaccine, however, had proved entirely harmless in thousands of cases. It is more than probable that the actual danger would begin if such occasional stray spores were allowed to germinate in the vaccine pulp through some serious fault in manipulation. It is conceivable that the vaccine pulp after removal from the calf or heifer, if not at once chilled and placed in a low temperature, or mixed with glycerin or other antiseptic, such as carbolic acid or chloroform, may form a very rich medium for anaërobic bacteria. Some carelessness or neglect just at this stage might prove disastrous if tetanus spores accidentally present should multiply. The epidemic in this country in 1902, reported by Willson¹⁴ and McFarland,¹⁵ may have been the result of some such occurrence. On the other hand, neglected vaccination wounds, or those in which improper bandages or shields favor anaërobiosis, may stim-

13. Centralbl. f. Prakt. Orig., 1904, xxxvii, p. 48.

14. THE JOURNAL A. M. A., 1902, xxxviii, p. 1147.

15. Jour. Med. Research, 1902, n. s. ii, p. 474.

ulate the germination of spores coming from without and lead to the occasionally reported sporadic cases following vaccination.

In the preparation of antitoxic and bactericidal sera, there are so many safeguards thrown around them, from beginning to end, that here also only gross negligence or some hitherto unforeseen occurrence could lead to the production of tetanus. Yet several outbreaks of tetanus occurred some years ago—one in this country and one in Europe—as a result of the use of antitoxin.¹⁶

The occurrence of tetanus after the subcutaneous injection of gelatin in uncontrollable hemorrhage caused consternation in medical and surgical circles some years ago. The cases were reported in 1902 and 1903. I find no reports later than the latter year. In 1903 Chauffard¹⁷ was able to report to the French Academy of Medicine as many as 18 cases collected from medical literature. Dieulafoy¹⁸ adds five cases to this list. I have made no attempt to bring together all the cases. The 23 above referred to are already too many, and show how the widely diffused use of a new remedy may lead to many nearly simultaneous fatal accidents. The explanation was very simple. Commercial gelatin, on examination, was found to contain tetanus spores. Thus Levy and Bruns⁴ found eight out of thirteen samples of gelatin infected with them. Krause¹⁹ failed to find his samples infected. Anderson⁵ reports one out of seven infected. Tuck⁶ found one out of six samples of French gelatin, one out of four samples of German gelatin and four out of five samples of English gelatin contaminated with tetanus. The gelatin was usually sterilized at the apothecary's and the process was insufficient to destroy the spores. In view of the fact that some of the spores in my cultures resisted boiling 40 to 70 minutes, the recommendations of the various writers who investigated the bacterial flora of commercial gelatin, or else had used gelatin in their practice are interesting.

Margoniner and Hirsch²⁰ expose the gelatin in 2 per cent. solutions to streaming steam for one hour. Krause¹⁹ recommends streaming steam for 30 minutes on five consecutive days. Holschmidt²¹ boils the 2 per cent. solution in a water bath for five or six hours. Anderson⁵ recommends boiling for at least 10 minutes, or else fractional sterilization on three successive days. The temperature at which this is to take place is not given. Falcioni⁷ calls attention to the uncertainties of discontinuous steaming, because in his experiments the spores failed to germinate in 2, 5 and 10 per cent. gelatin. He recommends 30 minutes, at 130 C., in the autoclave. Levy and Bruns⁴ recommend streaming steam for 40 minutes. They call attention to the dangers of using large flasks in place of test tubes, for the former become heated rather slowly. Finally, the commission²² appointed by the French Academy of Medicine recommend that the gelatin dissolved in 0.7 per cent. sodium chlorid solution be exposed, in bulk not exceeding 150 c.c., in an autoclave at 115 C. for 30 minutes.

There is sufficient variety in these recommendations to justify a more thorough investigation, even if the in-

jection of gelatin in surgery should not prove to do all that has been ascribed to it.

The possible association of tetanus with bacterial vaccines was demonstrated in the unfortunate outbreak at Mulchowal, India, in 1902. Only last year full abstracts of the reports of the investigating committees were published in English medical journals.²³ These inform us that at the place mentioned 107 persons were inoculated with Haffkine's plague prophylactic. Of these 19 were affected with symptoms of tetanus and died. The prophylactic consisted of a suspension of plague bacilli from agar cultures in salt solution and sterilized by heat. The 19 unfortunates were all inoculated with fluid from the same bottle. They were the first to undergo the treatment. The syringe was cleansed superficially after this bottle had been emptied and the rest were injected with the same syringe from other bottles of the same lot, but none contracted the disease. A dramatic incident occurred when the prominent persons of the locality at first hesitated to undergo the simple operation. Dr. Elliott, the physician in charge, bared his arm and was prepared to inoculate himself first. At this the people gave way and submitted to the injection. Dr. Elliott would have been among the victims.

Exhaustive investigations were made by an Indian Commission and by the Lister Institute in London. The records show certain irregularities which occurred during the administration of the vaccine, such as the dropping of forceps used to remove the cork upon the ground, etc. Both commissions, however, are inclined to refer the accidents to the contents of the bottle rather than to extraneous infection during the operation. It also seems to me that the evidence points in this direction. I have been unable to read the full report and learn of any investigations as to the mode of sterilizing the culture fluid in the laboratory at Bombay, where the plague vaccine was prepared.

My own experience, related above, opens up the possibility for the survival of tetanus spores in bouillon or agar, unless temperatures above 100 C. are used. It should also be borne in mind that tetanus spores are widely disseminated in India. Goodrich²⁴ states that in Bombay alone there were 1,955 cases of tetanus in five years. These do not include puerperal cases.

Before leaving this phase of the subject there should be mentioned, for the sake of completeness, the epidemics of tetanus in our large cities, following wounds from blank cartridges on Independence Day. The only experimental study of this subject which I have been able to find is by H. G. Wells.²⁵ Dr. Wells made an exhaustive bacteriologic study of 200 cartridges from five firms. Though several other anaërobes were encountered in cultures from them the tetanus bacillus was not detected.

The great resistance of tetanus spores concerns both the practicing physician and surgeon and the laboratory worker who is engaged in the preparation of biologic products for subcutaneous administration. As regards the surgeon, I do not believe that the usual disinfection by boiling or steaming at 100 C., such as may be resorted to away from hospitals need be placed under suspicion or discarded, but whatever has come in contact with fecal matter or with material undergoing putrefaction should be autoclaved at 110 C. to 115 C., unless the disinfecting action of the boiling water in which objects are immersed is increased by alkalis and other substances.

16. The outbreak ascribed to this country occurred in St. Louis in 1902, and was due to the presence of tetanus toxin in the diphtheria antitoxin. It was proved by a commission that the horse yielding the serum was in the incubation stage of tetanus. (Bolton and Fisch, *Trans. Amer. Physicians*, 1902, p. 463.)

17. *Bull. Acad. Med., Paris*, 1903, xlix, p. 549.

18. *Bull. Acad. Med., Paris*, 1903, xlix, p. 630.

19. *Berl. klin. Wochschr.*, 1902, xxxix, p. 673.

20. *Therapeut. Monatshefte*, 1902, p. 334.

21. *Münch. med. Wochschr.*, 1902, xlix, p. 12.

22. *Bull. Acad. Med.*, 1903, i, p. 805.

23. *Jour. Trop. Med. and Hyg.*, 1907, x, p. 33.

24. *Annals of Surgery*, 1897, xxvi, p. 710.

25. *Phila. Med. Jour.*, 1900, v, p. 1377.

It is the producer of biologic products who is most concerned in the occurrence of resistant tetanus spores. For if they may resist boiling for an hour, it is obvious that the autoclave is the only safeguard. Wherever tetanus antitoxin is being prepared, the necessary preparation of tetanus toxin to immunize horses makes great caution necessary. Whatever comes in contact with such toxin must be autoclaved, and the communication between the rooms where tetanus toxin is being prepared and those devoted to antitoxins should only be through the autoclave, so far as all apparatus is concerned. The occasional occurrence of tetanus among the horses of antitoxin plants may, in part, be due to the accidental escape of tetanus spores from the laboratory. Spore-containing toxins should not be injected and even filtered toxins should be treated with suspicion, as filters may become leaky at any time.

In the preparation of bacterial vaccines the danger is not altogether chimerical. My own experience with the tetanus spore, which successfully ran the gauntlet of the ordinary sterilization, and reappeared in the fully developed diphtheria culture in a Fernbach flask, is a good illustration. At that time autoclaves were not so generally used as they are now and it was my belief that the higher temperatures rendered the bouillon less satisfactory for toxin-production. So far as I know this belief has not been disproved, but the autoclave came, nevertheless, as a necessity, and it has come to stay. The occurrence emphasizes the importance of routine microscopic examination of all such material, testing it on small, susceptible animals and making subcultures wherever the product is to be used on the human subject.

It must be emphasized, however, that in spite of the wide distribution of tetanus spores over the world, and the gigantic amounts of biologic products in the form of sera and vaccines consumed annually the number of accidents which have occurred is excessively small and no one is likely ever to recur from the same causes. If accidents should occur they will be due to the erroneous impression still generally prevalent concerning the heat resistance of tetanus spores. The chief object of my communication is to aid in dispelling this error.

The prevention of tetanus should not rest with the attempts to destroy the spores, but go farther and determine, if possible, what the real habitat and the bacterial and other associations of this formidable species are. We have two ways of approaching this problem. One is to localize the bacillus by actual isolation, i. e., by finding it by means of bacteriologic procedures. The other is more indirect and consists in a detailed study of its biologic characteristics and those of closely related species, from which its affinities might be inferred.

As regards its occurrence, it is now well known that well-manured garden soil has yielded tetanus bacilli in the hands of various observers. The old theory derived from the French, which claims that the tetanus bacillus is a regular inhabitant of the intestines of the horse, and newer observations which extend this habitat to other species of domestic animals as well, seems to have found more or less acceptance. Thus, Sanchez Toledo and Veillon²⁶ found tetanus in the feces of four out of six horses and in the feces of one of two cows. Hoffmann²⁷ examined feces of rabbits, guinea-pigs, horses, cattle and sheep. Only one examination of 22 proved positive. This was in the feces of a horse. Pizzini²⁸ found tetanus

bacilli in the feces of peasants having much to do with horses.

The large cecum and double colon peculiar to the genus including the horse, in which the food after passing the small intestines is stored temporarily to permit absorption, serves well the purposes of anaerobes. This large reservoir may dilate rapidly during digestive disturbances, when fermentation is not kept under control and may require tapping to relieve the great distension. It would be a rather curious paradox if the animal, the most susceptible of all to tetanus toxin, should prove to be the primary host of the tetanus bacillus. We should expect the exact reverse and look for a relatively high immunity of the carrier.

Closely associated with this problem of breeding places of the tetanus bacillus is its dissemination over the globe and the presence of its spores in so many places outside the intestines of animals. The great resistance of the spores to the normal destructive influences of nature in part explains this dissemination. Climate enters as a factor, for tetanus is stated to be far more prevalent in warm climates. Yet Iceland at one time suffered severely from tetanus neonatorum.

The biologic characteristics of this organism are in some respects noteworthy. On account of the disagreeable odors which emanate from its cultures it may be classed among the putrefactive anaerobes, yet it has very feeble, if any, powers of liquefying coagulated blood serum and egg albumin, and it liquefies gelatine very slowly. The ordinary non-pathogenic putrefactive anaerobes possess these powers to a high degree. Indol may easily be demonstrated in its cultures, but not in those of the actively putrefactive types. These characters place it between the genuinely pathogenic and the putrefactive anaerobes. Some years ago I formulated the doctrine that among a given group of closely related bacteria those which became parasitic and pathogenic lost some or all of the fermentative and putrefactive functions belonging to more independent types. Judged from this standpoint, the tetanus bacillus has lost some and retained other characteristics of the putrefactive types and this would point to the digestive tract as a possible breeding ground. On the other hand, the presence of the tetanus bacillus in garden soil and in gelatin suggests much more extensive breeding places than the intestine, and it may be that it is capable of multiplying in symbiotic relation with other anaerobes wherever proteid material undergoes putrefaction. In fact, it is conceivable that it simply passes through the intestines in spore form without multiplying at all.

Another aspect of the subject well worth considering is the continued dissemination of this organism and the permanent infestation of regions originally free from it, through commercial and industrial agencies, just as certain territories in our country have become permanently infected with anthrax spores, thanks to the offal and residues washed down into streams from tanneries and hair factories. The wide distribution and consumption of gelatin infected with tetanus spores must certainly assist, quite effectively, in their dissemination wherever human ordure is used as a fertilizer, for the usual culinary treatment of gelatin can hardly be expected to kill tetanus spores. The same may be true of the wide dissemination of tetanus spores on vegetables, tubers, and fruits²⁹ transported by train loads from

26. La Semaine Med., 1890, x, p. 45.

27. Hyg. Rundschau, 1905, xv, 1233.

28. Riv. d'igiene e. san. pubbl., 1898, x, p. 170.

29. Only recently Rabinowitsch found the water in which strawberries sold in Berlin had been washed quite regularly infected with tetanus spores. Arch. f. Hygiene, 1907, lxi, p. 103.

south to north, from west to east, and as a general rule from the territories where tetanus may be considered most prevalent to those in which it is less prevalent.

Another agency in the distribution of tetanus spores over limited areas is the common housefly. Anyone who has occupied himself with the study of tetanus and other putrefactive bacteria, knows how a solitary housefly in a large room is quickly attracted by the offensive odors, and how persistent in its attempts to reach the culture fluid this insect is. Films spread on cover-glasses are quickly eaten by this pest, and in view of experiments made by Lord and others with tubercle bacilli I do not hesitate to assume that tetanus spores are not injured in their passage through the digestive tract of flies, and that the latter may carry this infection from house to house. There can be no doubt that with the mosquito and the rat, the housefly has much to answer for in civilized communities.

The theme on which I have discoursed at some length may seem to many a commonplace one and hardly worthy of notice. To one who has had the responsibility of the preparation of diphtheria antitoxin during the past 12 years, the subject appears of great importance, for the preparation of such therapeutic agents requires all the circumspection, care and knowledge which can possibly be bestowed on it. It is far easier to arouse the nervousness of the public than to allay it, and though the accidents that have followed directly or indirectly the use of biologic products are infinitesimal as compared with those of our railroads, yet the public is accustomed to the one and more or less indifferent to it, and very much disturbed by the other. The cause of rational, progressive medicine is distinctly retarded by accidents which would hardly cause a ripple if they occurred in industrial life.

My theme finally illustrates an occasionally observed fact in medicine. Whenever practice outruns the laboratory, and, more or less impatient, applies the latter's results to the prevention and cure of disease, it frequently deals with half truths whose application may be harmful. It is this sense of being surrounded by half truths which should stimulate us all not to rest content with them, but to use our efforts unremittingly until they have been made whole.

Original Articles

THE HOME TREATMENT OF PULMONARY TUBERCULOSIS.

ORVILLE HARRY BROWN, M.D.

Physician in Chief of the Missouri State Sanatorium,
MOUNT VERNON, MO.

INTRODUCTION.

In acute diseases, reactions to treatment (hygienic, medicinal and other) are often more or less prompt and decisive. In chronic diseases the reactions to treatment are, for the most part, slow and so indefinite as to cause a shadow of doubt as to the responsibility of the treatment, for either the good or bad termination. In acute diseases physicians generally recognize that the chances for recovery are greatly enhanced by perfect quiet. So firmly do they believe this that every movement possible is saved the patient. A nurse assists in the feeding, she bathes the patient in such a way as to worry him the least; everyone is excluded from the sick room, with the exception of the nurse and one or two of the

most intimate members of the family, and, in fact, everything is done to ensure quiet for the patient.

The prolonged course of chronic diseases, the hopelessness of the conditions, the resulting severe mental disturbances, the dread of the inevitable period of considerable duration when the victims are forced to take to their beds, have all been factors in causing physicians to recommend as active a life as could be tolerated without too much inconvenience. Thus it has been with tuberculosis. Most of the physicians, as well as the laity, up till recently, have considered tuberculosis as an incurable disease, and have only attempted to make the progress of the disease as slow, and the remaining days as livable, as possible. The treatment of tuberculosis in recent years has yielded such gratifying results that we can now say that, beyond question, tuberculosis is curable. This idea has not yet become generally disseminated. But we must change our opinions regarding the curability and the treatment of tuberculosis, and the sooner we do this the more lives we will save. Someone has pertinently said that "We must care for the consumptive in the right place, in the right way, and at the right time, until he is cured, instead of, as now, in the wrong place, at the wrong time, until he is dead."

The question of what to say when asked for advice by a consumptive is ever a puzzling one to most physicians. Just what advice is given very often, is too well known to make it of any force if repeated here. The writer sees so many patients who are doing the wrong thing, often on the advice of physicians, that he is prompted to write on the above topic.

PHYSIOLOGY OF TUBERCULOSIS.

The anatomy of the pathologic lesion of the disease is well known to all, but not so the physiology—and the physiology is of the extremest importance. Tubercle bacilli produce poison. When this goes into the system, by absorption from a lesion in the body or from a hypodermic injection, a definite physiologic reaction is induced. This reaction is responsible for the symptoms of tuberculosis. Wright, of London, and his assistants have found that exercise and massage of an infected area produce as definite changes in the blood as come from injections of tubercle poison, whereas this will not occur if the infected part is kept quiet. For this reason an organ the seat of an infection should be placed at rest.

In the light of Wright's discoveries the rest should be intercepted by sufficient work to cause an inoculation into the blood of a small amount of poison at not too frequent intervals. The rationale of this will be seen in a later paragraph. The corpuscles of the blood have the faculty of ingesting bacteria. The serum of the blood often has the property of agglutinating bacteria and of precipitating the toxin of the bacteria. These are some of the protective elements or immunity factors of the blood. There are others of which we know, and there are doubtless still others of which we do not know. It has been shown that these protective elements are profoundly influenced by bacterial toxins.

When the toxin first goes into the blood there is a decrease in at least some of the protective elements. The extent and duration of the decrease is slight or great, depending on the amount of toxin introduced and the ability of the blood to counteract it. This period of decrease, called by Wright "the negative phase," endures usually from a few hours to a few days. If during this