

afflicted with this disease who is in their care or has come under their observation within one week of such time. It shall be the duty of every person sick with this disease and of the authorities of public and private institutions or dispensaries, to observe and enforce all the sanitary rules and regulations of the Board of Health for preventing the spread of pulmonary tuberculosis.

(L. S) CHARLES G. WILSON, President.
EMMONS CLARK, Secretary.

It will be observed that this regulation limits itself to declaring that pulmonary tuberculosis is an infectious and communicable disease, to requiring its occurrence to be reported, and to insisting on the observation of the precautions of the Board for preventing the spread *not of the acute contagious diseases*, but of this one particular disease.

The nature of these precautions may be gathered from the following circular of the Board, entitled "Information for Consumptives and Those Living with Them."

HEALTH DEPARTMENT, CRIMINAL COURT BUILDING, CENTER,
WHITE, ELM AND FRANKLIN STREETS, NEW YORK.

Consumption is a disease which can be taken from others and is not simply caused by colds. A cold may make it easier to take the disease. It is usually caused by germs which enter the body with the air breathed. The matter which consumptives cough or spit up contains the germs in great numbers; frequently millions are discharged in a single day. This matter, spit upon the floor, wall or elsewhere, is apt to dry, become pulverized and float in the air as dust. The dust contains the germs, and thus they enter the body with the air breathed. The breath of a consumptive does not contain the germs and will not produce the disease. A well person catches the disease from the consumptive only by in some way taking in the matter coughed up by the consumptive.

Consumption can often be cured if its nature is recognized early and proper means are taken for its treatment. *In a majority of cases it is not a fatal disease.*

It is not dangerous for other persons to live with a consumptive, if the matter coughed up by the consumptive is at once destroyed. This matter should not be spit upon the floor, carpet, stove, wall, or anywhere except into a cup kept for the purpose. The cup should contain water so that the matter may not dry, and should be emptied into the closet at least twice a day and carefully washed with hot water. Great care should be taken by a consumptive that his hands, face and clothing do not become soiled with the matter coughed up. If they do become soiled they should be at once washed with hot soap and water. When consumptives are away from home, the matter coughed up may be received on cloths, which should be at once burned on returning home. If handkerchiefs are used (worthless cloths which can be burned are far better), they should be boiled in water by themselves before being washed.

It is better for a consumptive to sleep alone, and his bed-clothing and personal clothing should be boiled and washed separately from the clothing belonging to other people.

Whenever a person is thought to be suffering from consumption, the name and address should be at once sent to the Health Department, on a postal card with a statement of the facts. A medical inspector from the Health Department will then call and examine the person to see if he has consumption, providing he has no physician, and, if necessary, will give proper directions to prevent others from catching the disease.

Frequently a person suffering from consumption may not only do his usual work without giving the disease to others, but may also get well if the matter coughed up is properly destroyed.

Rooms that have been occupied by consumptives should be thoroughly cleaned, scrubbed, whitewashed, painted, or papered before they are again occupied. Carpets, rugs, bedding, etc., from rooms which have been occupied by consumptives, should be disinfected. The Health Department should be notified, when they will be sent for, disinfected and returned to the owner free of charge, or, if he so desires, they will be destroyed.

By order of the Board of Health,
CHARLES G. WILSON, President.
EMMONS CLARK, Secretary.

The State Board of Health of Pennsylvania has contented itself, so far, with adopting a resolution advising all local boards to place tuberculosis on the list of communicable diseases, to be reported, and

issuing a precautionary circular for the information of local boards, and also of those who may be suffering from the disease. By such sufferers these circulars are, as a rule, gratefully received. This circular is No. 28, entitled "Precautions Against Consumption" and treats of the history and nature of the disease; how the disease is spread or acquired; precautions with regard to cattle; precautions to be observed by the patient; disease germs; precautions to be taken in the sick-room; precautions to be taken after the death of the patient; and precautions to be taken by the proprietors of public houses and public conveyances.

THE ANTITOXIC AND BACTERICIDAL PROPERTIES OF THE SERUM OF HORSES TREATED WITH KOCH'S NEW TUBERCULIN.

Read at the Twenty-third Annual Meeting of the Mississippi Valley
Medical Association, held at Louisville, Ky., Oct. 3-8, 1897.

BY CARL FISCH, M.D.
ST. LOUIS, MO.

All attempts at establishing a serotherapy in tuberculosis have hitherto failed, that means, if we understand by serotherapy a specific prophylactic or curative treatment, like the one established in diphtheria or tetanus. So decided and pronounced has this failure been that in the mind of many observers a strong prejudice has been created, a prejudice that appears the more justifiable since commercialism has not hesitated in exploiting so promising a field. We would however be very hasty in drawing from these failures the conclusion that serotherapy in consumption is not a thing to be hoped for, as has been done by many writers. We can not be too chary in making final statements, a postulate that at this very time emphasizes itself with particular weight by the discovery made by Kitasato of an antitoxic typhoid serum. Has it not been for some time past one of our axioms, that in typhoid and cholera only bactericidal and no antitoxic properties were developed? The less we try to encase new ideas, and serotherapy is a new idea, in the forms of old conceptions, the less frequently we will have to retrace our steps. No metewand has as yet been discovered to point out the limits and boundaries of this new idea; whoever talks about the limits of serotherapy confesses that he does not or will not understand its origin.

For these very reasons it is an unpromising task to foretell by logic reasoning, whether or to what degree serum treatment will influence tuberculosis. Nobody ever expected that it would bring about a *restitutio ad integrum* in advanced cases, or redress the ravages of septic complications. It is certainly absolutely erroneous to insist that the anatomo-pathologic phenomena of pure tuberculosis, are not indicative of a toxic process which might be amenable to antitoxic impressions. Such intoxication exists from the very first hour, I might say, of the beginning of tuberculous infection, a fact that is not only evidenced by histologic changes, but that can also be proven by physiologic reactions. To say that the early tuberculous changes are simply of an inflammatory character expresses only a morphologic phenomenon. Physiologically they are as pronouncedly caused by bacterial toxins as are any other bacterial intoxications. It is true this toxic inflammatory process is little noticeable in its early stages and becomes mostly chronic, gradually undermining the vital vigor and leading to

fatal loss of substance or secondary infections (in fact, very few persons die of chronic tuberculosis), but in this very chronicity the battle waged between the human organism and the array of bacterial toxins expresses itself; very often the former remains victorious perhaps in a majority of cases. In our language such a victory means immunization although only for the time being.

It is not here the place to enter more fully into these exceedingly interesting questions. I had to touch upon them because it has ever and again been contested that theoretically there were no prospects for serotherapy in this disease. Valuable remarks regarding this topic may be found in an able paper of Joseph McFarland.¹

But we would be wrong if we attributed this reserve to well conceived and understood pathologic considerations alone; behind them there lurks a preconceived idea of self-limitedness, and above all a mysterious predisposition for the disease. This hereditary predisposition would be well worth to be looked into a little more thoroughly; I can not do it here, and must confine myself to the statement that a scientific base for the tubercular predisposition still is wanting.²

Not mentioning those attempts at putting forth an antitubercular serum that were only prompted by mercenary motives, the number of honest workers in this field is quite large. Since Richet and Hericourt first began their experiments an enormous amount of persevering and unselfish work has been done. I will only mention the names of Courmont, Babes, Niemann, Maragliano, Schweinitz, etc. Admitting that there are considerable differences between the several methods employed by these investigators, entering into which would lead us too far here, there is one source of error common to all, that is the material used for immunizing the animals which were used for the purpose. If we look over the laborious experiments of Koch to establish immunity by means of tubercle bacilli or of their products, we find that the chief difficulty was to cause the tubercle bacilli to be absorbed by the tissues or to chemically so act on the bacilli that their immunizing ingredients were contained in a fluid extract. The peculiar morphologic and chemic constitution of the tubercle bacilli made, indeed, all these experiments unsuccessful. Koch had finally to destroy the morphologic entity of the bacilli in order to obtain unobjectionable results. In other words the essential toxins (some writers it is true, assert that there are no essential tubercle toxins) are not excreted like they are in cultures of diphtheria bacilli, but they are to the far greatest extent enclosed within the membrane of the bacterial cell. The culture fluids contain none, or very little of these specific toxic substances; they may be injected in comparatively large doses into animals without causing serious damage.³ We may add right here that it seems that there are produced a number of different toxic substances, at least this would best explain the contradictory results of some observers; but we must not forget that ferments or enzymes, like the bacterial toxins, are very unstable compounds and are easily changed in their chemic nature by all kinds of artificial procedures. It is, therefore, more than likely that the different bodies isolated from tubercle bacilli or their culture media, are not pre-existing, but represent ingredients of the former in a changed form.

Surely this holds good for the old tuberculin, which has mostly been used as an immunizing agent. How

little this fluid represents the active principles of the live tubercle bacillus is well illustrated by the following observation. If some of the dead and extracted bacilli which remain as residue after the preparation of tuberculin are injected into suitable animals, they not only cause the formation of typical tubercles, but even prompt these animals to yield a typical tuberculin reaction. It is well known, furthermore, that this tuberculin reaction, the nature of which has by no means as yet been explained, may be obtained by several other similar bacterial compounds (proteins) and even by heterogeneous albuminous bodies (deutero-albumoses). No matter in which way the tuberculin was prepared it is *a priori* impossible that the serum of animals immunized against it possesses any antitoxic properties as far as the tuberculosis toxins are concerned. A certain antituberculinic power may be exhibited by it (this is apparent especially by experiments made by Schweinitz⁴, Babes⁵ and others), and by it some influence on tuberculous processes may be now and then explained. In general, the results obtained with such a serum have been discouraging. The same obtains for those modifications of antitubercular sera, for the preparation of which in addition to tuberculin cultures of the bacilli, dead or alive, have been utilized. As said above these bacilli are very slowly resorbed, the greater part of them is ejected in the pus of abscesses formed at the site of the injection. It must not be denied, however, that in some instances the results thus reached were fairly promising. This refers especially to the work of Niemann⁶ and Babes⁷, who really repeatedly immunized guinea pigs in this way against inoculation with living bacilli. This proves that the serum prepared by them possessed distinct antitoxic (according to Babes even bactericidal) properties. But they also operated only with a part of the active principles of the tubercle bacillus, and accordingly the outcome of their labors lacks consistency and certainty. In no case out of the great number of respective investigations was a stage reached in which the observer could with certainty foretell the result of an experiment.

That both antitoxic as well as bactericidal potencies must be qualities of an antitubercular serum, is shown by the well-known phenomenon that we sometimes have to deal with an infectious, mostly with a toxic type of the disease; that living bacilli, furthermore, as such are less apt for the production of such a serum than dead ones (that means bacilli easier accessible to disintegrating influences) is indicated by the enormously larger toxicity of dead bacilli⁸. It may be well in this connection to mention the important fact that from the tuberculous organs of infected animals an extract can be prepared, that while being exceedingly toxic when injected in gradually increasing doses into guinea pigs, in a short time immunizes them against the introduction of virulent cultures⁹.

If so it goes without saying that "antituberculin sera" are not what must be claimed from an antitubercular serum; there are certain direct drawbacks attached to them, that under circumstances have proved very obnoxious. In the first place the assimilation of the tuberculin by the animal organism is a slow process; it may happen that the serum of these animals contains unchanged tuberculin instead of antituberculin. The following experiment illustrates this fact: A healthy guinea pig received in seven doses during twenty days as much as 10 c.c. of tuberculin. Ten days after the last injection some blood was drawn

from this animal; 1 c.c. of the serum of this blood was sufficient to produce a typical and very violent tuberculin reaction in a tuberculous guinea pig. This phenomenon is at the bottom of what in the literature is known as transmitted tuberculin-action. Its undesirability is evident.

TABLE 1.—Influence of T.R. serum on the temperature of healthy guinea pigs.

Date.	Number of guinea pig.	Weight in grams.	Amount of serum injected.	Temper. before injection.	Three hours later.	Six hours later.	Nine hours later.	Twelve hours later.
July 16. . .	52	750	0.25 c.c.	101.6	100.8	101.0	101.2	101.5
July 16. . .	53	640	0.50 c.c.	102.1	101.0	101.5	101.8	102.2
July 16. . .	54	680	1.00 c.c.	101.8	101.2	101.2	101.4	101.6
July 16. . .	56	706	2.00 c.c.	101.7	100.6	100.8	101.0	101.6

TABLE 2.—Effect of normal horse serum on the temperature of healthy guinea pigs.

Date.	Number of guinea pig.	Weight in grams.	Amount of serum injected.	Temper. before injection.	Three hours later.	Six hours later.	Nine hours later.	Twelve hours later.
July 17. . .	55	714	0.50 c.c.	102.2	101.6	101.6	102.0	102.4
July 17. . .	57	685	1.00 c.c.	102.4	101.3	101.6	102.4	102.2

TABLE 3.—Guinea pigs, after previous immunization with T.R. serum, inoculated with a fatal dose of tubercle bacilli.

No.	Weight July 5.	Weight Aug. 3.	Inoculated with fatal dose of T.B. Aug. 3.	Weight Sept. 20.	Remarks.
17	850	867	Subcutan.	880	Sept. 20, perfectly healthy.
20	740	748	Subcutan.	764	Sept. 20, perfectly healthy.
21	874	888	Intraperit.	888	Killed Sept. 20. No lesions.
24	560	571	Not inocul.	588	Healthy.
25	674	692	Not inocul.	712	Healthy.
22	...	721	Subcutan.	...	Died Aug. 27.
23	...	856	Subcutan.	...	Died Aug. 24.

TABLE 4.—Immunization experiment 1.25 c.c. serum T.R.

No.	Weight July 5.	Weight Aug. 3.	Fatal dose of T.B. Aug. 3.	Weight Sept. 20.	Remarks.
18	716	724	Inoculated	723	Extensive infiltration.
19	685	698	Inoculated	696	Extensive infiltration.
22	560	575	Inoculated	575	Died Aug. 23.
38	612	621	Not inocul.	629	...
39	451	468	Not inocul.	476	...

TABLE 5.—Immunization experiment 2.5 c.c. of serum.

No.	Weight July 5.	Weight Aug. 3.	Fatal dose T.B.	Weight Sept. 20.	Remarks.
60	672	675	Inoc. Aug. 3.	677	Perfectly healthy.
61	457	471	Inoc. Aug. 3.	475	Perfectly healthy.
62	489	496	Inoc. Aug. 3.	501	Perfectly healthy.
63	723	729	Not inoculat'd	738	Perfectly healthy.
64	594	617	Not inoculat'd	629	Perfectly healthy.

TABLE 6.—Serum and virus injected (mixed).

No.	Weight July 14.	Mode of inoculation.	Weight Sept. 16.	Remarks.
1	456	T.B. and ½ c.c. ser. subcut.	469	Healthy.
2	567		581	Healthy.
3	496		517	Healthy.
37	712		730	Healthy.
88	591	T.B. and ½ c.c. ser. intraper.	612	Healthy.
39	623		627	Healthy.
35	720		731	Healthy.
66	635		649	Healthy.
67	587	T.B. and 1 c.c. ser. subcut.	610	Healthy.
68	421		487	Healthy.
69	566		575	Healthy.
70	578		592	Healthy.
71	703	T.B. and 0.1 c.c. ser. subcut.	584	Died August 20.
72	627		...	Large infiltration.
73	651		...	Died Sept. 6.
81	561		...	Died August 7.
32	622	Fatal dose T.B. alone.	...	Died August 3.
33	786		...	Died August 12.
84	612		...	Died August 5.
35	659		...	Died August 1.
36	477	T.B. and 0.25 c.c. Paquin's ser. subcut.	...	Died July 30.

TABLE 7.—Serum and virus injected separately.

No.	Weight July 19.	Mode of inoculation.	Weight Sept. 12.	Remarks.
11	425	T.B. and 0.25 c.c. serum.	439	Healthy.
12	553		576	Transitory gland enlargement.
13	496		519	Healthy.

TABLE 8.—Treatment begun four days after inoculation.

No.	Inoculated with fatal dose of T.B.	Weight July 20.	Begin. of serum injection 0.25 c.c. every other day.	Weight Sept. 24.	Remarks.
4	July 20. . .	560	July 24. . .	572	Perfectly healthy.
5	July 20. . .	544	July 24. . .	548	Perfectly healthy.
6	July 20. . .	489	July 24. . .	500	Perfectly healthy.
30	July 20. . .	621	July 24. . .	629	Perfectly healthy.
40	July 20. . .	576	July 24. . .	587	Perfectly healthy.
41	July 20. . .	611	July 24. . .	619	Perfectly healthy.

TABLE 9.—Treatment begun seven days after inoculation.

No.	Inoculated with fatal dose of T.B.	Weight July 20.	Begin. of serum injection 0.25 c.c. every other day.	Weight Sept. 24.	Remarks.
7	July 20. . .	476	July 27. . .	482	Healthy.
8	July 20. . .	496	July 27. . .	503	Healthy.
9	July 20. . .	521	July 27. . .	586	Healthy.
10	July 20. . .	546	July 27. . .	550	Healthy.
11	July 20. . .	488	July 27. . .	499	Healthy.
12	July 20. . .	517	July 27. . .	523	Healthy.

TABLE 10.—Treatment begun ten days after inoculation.

No.	Inoculated with fatal dose of T.B.	Weight July 21.	Begin. of serum injection 0.25 c.c. every other day.	Weight Sept. 24.	Remarks.
13	July 21. . .	610	July 31. . .	612	Healthy.
14	July 21. . .	528	July 31. . .	529	Healthy.
15	July 21. . .	477	July 31. . .	479	Swelling of inguinal glands.
16	July 21. . .	531	July 31. . .	534	Healthy.
17	July 21. . .	601	July 31.	Killed Sept. 3.
18	July 21. . .	576	July 31.	Killed Sept. 3.

TABLE 10a.—Treatment begun fourteen days after inoculation.

26	July 21. . .	523	Aug. 3.	456	Glandular swell'g, ulceration.
28	July 21. . .	614	Aug. 3.	Died Sept. 4.
29	July 21. . .	539	Aug. 3.	474	All signs of tuberculosis.

TABLE 10b.—Controls; not treated.

42	July 21. . .	507	Not treated.	Died Aug. 15.
43	July 21. . .	563	Not treated.	Died Aug. 18.
44	July 21. . .	492	Not treated.	Died Aug. 11.

TABLE 10c.—Controls; treated with Paquin's serum.

45	July 21. . .	516	July 25.	Died Aug. 13.
46	July 21. . .	476	July 25.	Died Aug. 14.
47	July 21. . .	567	July 25.	Died Aug. 10.

TABLE 11.—Showing effect of tuberculin injection after six weeks of treatment.

No.	Date of injection of 0.1 tuberculin.	Temper. at time of injection.	Three hours later.	Six hours later.	Nine hours later.	Twelve hours later.	Fifteen hours later.	Eighteen hours later.
13	Sept. 12, 10 A.M.	101.8	101.9	101.8	102.1	101.8	102.0	101.6
14	Sept. 11, 2 P.M.	102.3	102.2	102.0	102.4	101.8	101.9	102.2
16	Sept. 14, 8 A.M.	102.0	102.0	102.0	102.2	102.0	102.2	102.4

TABLE 12.—Showing the effect of serum treatment on the temperature. First injection July 31, 12 A.M.

No.	July 29, 8 A.M.	July 29, 8 P.M.	July 31, 8 A.M.	July 31, 8 P.M.	Aug. 1, 8 A.M.	Aug. 1, 8 P.M.	Aug. 3, 8 A.M.	Aug. 3, 8 P.M.	Aug. 5, 8 A.M.
13	103.6	104.4	104.0	103.6	103.0	102.6	101.8	102.2	101.6
14	104.2	104.8	103.8	103.0	102.2	102.6	102.0	102.4	102.0
16	104.5	105.2	104.8	104.0	103.2	101.8	102.4	102.0	102.2

TABLE 13.—Test for bactericidal property of the serum.

Contact between TB and serum lasted hours.	1 c.c. of the T.B. Serum mixture injected intraperitoneally into guinea pig.	Date of injection.	Weight Sept. 20.	Remarks.
1	48 (weight 520)	August 5.	...	Died Aug. 21.
2	49 (weight 486)		...	Died Aug. 17.
3	50 (weight 578)		...	Died Aug. 20.
5	51 (weight 507)		516	No signs of disease.
8	74 (weight 495)		519	Healthy.
12	75 (weight 475)		489	Healthy.
24	76 (weight 503)		517	Healthy.

TABLE 14.—Inhibition of tuberculin reaction by means of 0.1 c.c. serum.

Number of guinea pig.	Injected with.	Temper. before injection.	3 hours later.	6 hours later.	9 hours later.	12 hours later.	15 hours later.	18 hours later.
74. Tuberculous for 2 weeks.	0.1 tuber. and 0.1 serum.	103.9	103.8	104.0	103.6	103.8	104.1	103.9
75. Tuberculous for 3 weeks.	0.1 tuber. and 0.1 serum.	102.4	102.6	102.4	102.8	102.2	102.6	102.4
76. Tuberculous for 10 days.	0.1 tuber. and 0.1 serum.	103.2	103.4	103.4	103.2	103.6	103.0	103.0
77. Tuberculous for 2 weeks.	0.1 tuberc.	103.0	103.0	103.6	104.2	104.8	104.6	103.8

TABLE 15.—Repeated toxin reaction in the same animal.

No. of guinea pig.	Injected with	Date of injection.	Temper. before injection.	3 hours later.	6 hours later.	9 hours later.	12 hours later.	15 hours later.	18 hours later.
78. Tubercul. for about 20 days	1. c.c. toxin	9-1	102.8	103.8	104.2	104.3	104.6	104.2	103.8
79. Tubercul. for 16 days	"	9-4	103.2	104.4	105.0	104.8	104.8	104.2	103.6
78.	"	9-4	103.0	104.6	105.4	105.0	105.2	104.2	103.8
79.	"	9-4	102.6	103.8	104.6	104.4	104.4	104.0	103.6
78.	"	9-8	103.4	104.8	105.6	105.2	105.4	104.8	104.0
79.	"	9-8	102.8	104.2	104.4	104.8	105.0	104.6	104.0
78.	"	9-11	102.6	104.0	104.6	104.4	104.0	104.2	103.6
79.	"	9-11	103.4	104.4	104.8	105.0	105.0	104.2	103.6
78.	1.5 c.c. toxin	9-14	102.4	104.8	104.8	105.0	104.6	104.4	103.6
79.	"	9-14	103.2	104.2	104.6	104.8	104.2	104.0	103.0
78.	"	9-17	103.0	103.8	104.2	104.8	104.6	104.6	10.40
79.	"	9-17	102.4	103.6	103.8	104.6	104.2	104.0	103.4

Again, it is little known that bacterial proteins in glycerinic extracts, when administered for any length of time, invariably tend to produce a chronic nephritis. Niemann¹⁰ first called attention to this fact, and I found it confirmed in two horses which for some months had been treated with high doses of tuberculin. It is not impossible that the fatal effects, which these sera sometimes have on animals, are due to uremic products retained in the blood serum. Babes¹¹ saw guinea pigs die from the injection of 0.5 c.c. of such a serum; Rutkowski¹² relates similar accidents in his report on Vicquerat's antitubercular serum. I myself saw repeatedly guinea pigs die in a very short time from the injection of 0.5 to 1 c.c. of Paquin's serum. The autopsy (death in diastole) did not reveal any definite cause of death.

The foregoing somewhat lengthy remarks were necessary in order to show that the solution of the tuberculosis serum problem depended upon the discovery of some means of making the tubercle bacilli with all their constituents easily resorbable. I did not fail at once to see that with Koch's new tuberculin, T. R.,¹³ this means was given, and immediately set to work to follow out this idea. But I would not like to be understood as if this work claimed to be something original; logically the thought was bound to offer itself, and in addition to this, Koch himself had insinuated it. While my experiments were going on, I had the satisfaction to hear that Behring¹⁴ was following the same lines, though no details whatsoever about his investigations have as yet reached this country.

It need not concern us here that at the present time a hot war is raging as to the therapeutic value of this new tuberculin; in contradistinction to other observers,¹⁵ I can confirm Koch's statement about its immunizing properties toward animals. But the salient point was that at last in it we had a substance which exhibited, in full and unchanged, all of the toxic ingredients of a tubercle bacillus. We have seen before that the culture media of tuberculosis cultures contain only a very small amount of toxic bodies, most likely the outcome of disintegration of the bacilli.¹⁶

If, therefore, a conclusion *per analogiam* was allowed, this new tuberculin (T. R., I shall henceforth call it), by immunizing animals was likely to produce the desired antitoxic effects, if such effects could be obtained altogether. Within the limits of our present knowledge no other means of doing this could be conceived.¹⁷ I began experiments in this direction, and the following remarks will give their results:

According to Koch's directions, a greater part of the tuberculous toxins is excluded under the name T. O.; this T. O. contains those toxins that are contained in the adhering traces of culture media, as well as those that easily are extracted from the membranes of the bacilli. They do not seem to have a great immunizing power, but are exceedingly toxic and resemble in their effects, in many regards, the old tuberculin. But try as I might, I could not convince myself as to the logical necessity to exclude this part of the toxins from the immunizing process, so much the less since in my animals I did not need to be afraid of any, and even very severe, reactions. The same, I thought, applied to the fraction of toxic substances contained in the culture media. To express myself candidly, I did not want to take any chances in omitting some toxic body that afterward perhaps might prove of intrinsic value, although I knew that T. R. alone would immunize my animals against these substances. I used only strong and perfectly healthy horses.¹⁸

The way in which I proceeded may be described as follows: I began with the injection of 1 c.c. of T. R., which did not cause any reaction whatsoever; in the subsequent injections, which were made about every seven and ten days, the amount was about doubled each time until 30 c.c. of pure T. R. were reached. The reactions so far were very slight, the temperature never rising more than 1.5 degrees F. At this stage I commenced adding small amounts of T. O., as well as an aqueous extract of the nutrient agar; the reactions were very severe, sometimes reaching perfect prostration. Mostly a profuse diarrhea set in; after a temporary fall the temperature rose to 104 and 105 degrees F. Loss of appetite occurred, etc. In four or five days these symptoms disappeared. Sometimes abscesses formed, caused by some undestroyed tubercle bacilli. Gradually and cautiously I reached a combined dose of 75 c.c. of T. R. and 30 c.c. of T. O. The indications are, however, that much higher amounts will be tolerated, and I do not propose to stop before external reasons call for a halt. Both preparations, T. R. and T. O., were prepared in my laboratory, and the culture I used was of such a virulence that the *dosis minima*, when injected into the abdominal cavity of a guinea pig (about 500 grams), killed the animal within ten to fifteen days. As *dosis minima* I came to consider one loopful of an emulsion obtained by thoroughly triturating one loopful (1 mg.) of a four weeks agar culture with 1 c.c. of sterilized water. Smaller doses produced a protracted course of the disease; the latter then invariably attacked the lungs. The toxic power of this culture was so great that about 16 mg. of the dried and finely triturated bacilli killed, within twenty-four hours, guinea pigs of the above average weight. Therefore, if with Behring we call *m* the fatal dose of toxin for one gram of guinea pig, my culture possessed a toxicity of 30,000 t. m. I tested its toxicity during several generations, but did not find any material deviations. Cultures of a different origin showed only a potency of 400 and 2,000 respectively. A culture of

aviary tuberculosis goes as low as 260. We must not lose sight of the fact that these figures only hold good for guinea pigs.

The first blood was drawn after a T. R. dose of 50 c.c. (+ 25 c.c. T. O.) was reached, and with the serum obtained from this blood the following experiments were made. I will remark, however, that the serum from later bleedings (after larger doses of the immunizing fluid had been administered) showed in all essentials the same characteristics, only in an intensified degree. For my experiments I used guinea pigs, monkeys, and to a certain extent rabbits. I preserved my serum by the addition of camphor, 0.5 per cent. phenol or 0.3 per cent. trikresol. The action of the serum on a healthy animal is only noticeable by a slight fall of temperature two or three hours after the injection (Table 1); this fall of temperature ranges from 0.5 to 1 degree. Comparative experiments (Table 2) with normal horse serum demonstrated, however, that here too the same phenomenon could be observed. The amount injected varied from 0.25 c.c. to 2 c.c. Otherwise, no local or general reaction occurred.

In order to determine the presence of any immunizing power of our serum, in one series of experiments (Table 3) five guinea pigs were treated during thirty days with repeated injections of .25 c.c. of the serum; they received altogether 4 c.c. of serum each. After thirty days three of them were inoculated with the fatal dose of tubercle bacilli, the two remaining ones being kept as controls. At the same time two fresh animals received the same fatal dose of bacilli. The result was that after twenty-four, respectively twenty-one days, the two non-treated animals died with the typical lesions of tuberculosis, while the three inoculated ones, as well as the two controls, remained healthy and continued to gain in weight, the same as they had done during the serum treatment. After six weeks one of the infected animals was killed; the autopsy did not reveal any lesions whatsoever, neither at the point of injection, nor elsewhere.

Two other sets of five animals each were subjected to similar conditions, only the amount of serum and number of injections varying. One series (Table 4) received during thirty days five injections of .25 c.c. of serum each. Of three animals of this series inoculated with the fatal dose of tubercle bacilli, one died after twenty days; the two others showed extensive infiltration around the point of injection, but no ulcerations. They did not lose in weight. Whilst this experiment shows that the quantity of serum was insufficient for complete immunization, its effect is nevertheless very apparent.

The third series was treated during the same length of time with five injections of .50 c.c. each. Then three of them were inoculated. All animals remained well and continued to gain in weight (Table 5).

Though these experiments comprised only seventeen animals, the evidence brought out by them may well be considered conclusive in view of the fact that even an intraperitoneal inoculation (Table 3, No. 21), which otherwise invariably results fatally in a short time, did not cause any lesions whatsoever.

Naturally, as the next step in my investigations, the question offered itself, how the serum would influence tuberculous infection, when applied at the very moment of infection. Various amounts of serum were therefore mixed with the fatal dose of bacillary emulsion, the mixture being injected subcutaneously or into the abdominal cavity. Of three guinea pigs

which in this way received 1 c.c. each, not a single one showed any signs of infection; the same obtained for six others into which 0.5 c.c. each was injected and for the third set of three to which was given .25 c.c. each. When I lowered the dose to .10 c.c. the results became valueless (Table 6). As controls for this experiment two sets of three animals each served, one being inoculated simply and left without treatment, while the second set received with the bacilli .25 c.c. of Paquin's antitubercle serum. All six animals died within the usual time, two of the last (Paquin) set before the others.

We will see later on that our serum possesses very decided bactericidal properties. For this reason the experiments of the last series had to be varied so that bacilli and serum were injected at the same time, but each for itself, and in a different place. In this way three guinea pigs were treated, receiving the virus on the back, and the serum (.50 c.c.) on the abdominal aspect, as nearly as possible at the same time. They remained in perfect health, except No. 12, which showed, eight days after inoculation, a slight enlargement of the inguinal glands. The latter disappeared, however, in a short time, and the animal is as healthy today as are its mates (Table 7). After these tests the most difficult problem remained to be solved; how far advanced may a case of guinea pig tuberculosis be, in order to be amenable to a curative treatment by this serum? The number of my experiments bearing on this question is, I confess, but limited; I could convince myself that with almost absolute certainty one succeeds in saving the life of the animal when treatment is begun within the first ten days after inoculation with my culture. This time limit reached, the results became uncontrollable. I instituted treatment in several series four, seven and ten days after inoculation; injections (uniformly .25 c.c.) were given regularly every other day for four weeks; after that time one injection per week was deemed sufficient. Of eighteen animals I have lost, until the present date, not a single one, though in one an enormous glandular enlargement has developed. The characteristic ulcerations at the sites of inoculation are absent, and the temperature is normal.

Although I would not like to appear over-confident, the time elapsed since treatment was begun being only two and one-half months, I may safely assert that I consider those animals as recovered. In three of them I made the routine tuberculin test after six weeks of treatment without obtaining a reaction (Tables 8 to 11). Wherever ulcers had formed before the treatment they healed readily, no symptoms remaining to indicate a pathologic condition. The temperature was easily reduced to normal (Table 12); the weight kept steady or increased slightly.

Two animals of series 10 were sacrificed after seven weeks, to enable me to study the pathologic anatomy of the diseased organs. The liver showed those peculiar cicatricial ridges described by Koch as characteristic after T. R. treatment. The spleen in one case was extraordinarily contracted, etc. In one word, everywhere successful attempts at restitution or at least at encapsulation were obvious, the latter especially in diseased lymph glands. A description *in extenso* of these very interesting changes I must reserve for some future time, after my animals have been observed for a longer period. As controls, I used again some animals simply inoculated with bacilli, and some others which in addition received the benefit of the Paquin

treatment. All of these animals died in due time.

For brevity's sake I omit to mention a number of other experiments destined to investigate the protective and curative potency of the T. R. serum. Those that have been reported are more than sufficient to establish the fact that this serum not only protects guinea pigs against infection, but that it is too, of a very powerful curative potency.

Very gratifying was also the outcome of some experiments made on monkeys (belonging to the genus *Cebus*, of the order of the *Platyrrhini*). On July 22, two of them were inoculated with .25 c.c. of bacillary emulsion into the abdominal cavity. While one served as control, the other was treated to regular injections every other day, of .50 c.c. of T. R. serum; this treatment was begun the day after inoculation. Very soon, in the control animal, high temperature set in (rising to 105 and 106 degrees), emaciation became visible, and on September 10 death occurred from the most extensive visceral tuberculosis I ever saw. The lungs were not affected at all. His more fortunate mate is today alive and healthy, and did at no time exhibit any symptoms of infection. His temperature remained perfectly normal, his weight increased slightly and some days ago he did not react at all after .15 c.c. of the old tuberculin was injected subcutaneously.

Very satisfactorily, too, resulted an experiment on two other monkeys, into the trachea of which, after tracheotomy had been performed, .25 c.c. of bacillary emulsion was injected. Treatment of one of them was begun immediately after inoculation (August 16) in the way described in the former experiments. The control animal died September 5 with very extensive lesions of the larynx, lungs, liver and the whole lymphatic system; an enormous tuberculous ulcer had developed at the place where tracheotomy was performed. Emaciation was very marked, as well as the anemia. In contradistinction, the other animal kept a steady temperature and weight, and offered no sign of disease, except a small ulceration of tuberculous nature at the place of incision; I feel sure that prolonged treatment will cure him entirely.

For certain reasons I would like to omit here a report of experiments with intraocular inoculation of rabbits. The well-known uncertainty of such experiments arising from very marked differences in the susceptibility of these animals is an element that prevents conclusive deductions. May it, however, be said that when inoculation and serum injection were practiced at the same time, in no case an infection was effected. The results varied whenever four or more days intervened between the two.

However tempting and alluring the reported results may appear to one uninitiated into the deceptive phenomena and phases of experimental tuberculosis, I will make haste in accentuating the fact, that *per se* they do not form conclusive evidence as long as the animals have not been observed for a longer period (five to eight months). In order not to be misunderstood, I must repeat that the period of my observations extends only over two and one-half months. But combined with the following considerations they form an absolutely safe stronghold. If the T. R. serum acted specifically, this must be due to antitoxic or bactericidal properties; it became necessary, therefore, to demonstrate the latter.

The slowness of growth as well as their peculiar cultural arrangement compelled me to submit the

tubercle bacilli to the following procedures, which entirely differ from the usual method of determining the bactericidal power of a fluid. A number of sterile test-tubes were filled each with 5 c.c. of fresh T. R. serum. A few drops of an emulsion of tubercle bacilli were added to each of these tubes, whereupon the whole series was put into the incubator. After the lapse of a certain time the single tubes were removed and 1 c.c. of their contents injected intraperitoneally into healthy guinea pigs. Table 13 gives the results *in nuce*. It was found that a contact of the tubercle bacilli with the serum during five hours, was sufficient to destroy their vitality, or at least to impair their power of resistance so much, that the animal organism could easily rid itself of them.

The only attempt at determining this bactericidal power of an antitubercle serum, that I could find in the literature, was made by Babes,¹⁹ but the bacilli in his case were killed only after a contact of twelve days duration. I do not know but what the addition of a preservative will decrease this power in my case to a certain degree.

In the search for antitoxic properties, the customary methods of combining the serum with a certain amount of old tuberculin (either fatal or just sufficient to bring about the characteristic tuberculin reaction) offered itself first. Babes and Schweinitz in this way proved the "antitoxic" nature of their sera. So did Niemann. But according to what has been said above, the only thing proven by these tests is their antituberculinic nature, which will be present, too, in a really antitoxic serum, but at the best only forms a part of its potency. That, by the way, not even this antituberculinic quality is possessed by some of the "antitubercle" sera, has been shown by Behring (l. c.), who found that Maragliano's serum is perfectly void of it. As to Paquin's antitubercle serum, I repeatedly came to the very same negative result.

How my T. R. serum behaves in this regard will be seen from table 14. I found that .50 c.c. of it is sufficient to save a tuberculous guinea pig from the fatal dose (.20 c.c.) of tuberculin, and that .1 c.c. prevents the tuberculin reaction (.10 tuberculin). The tuberculin that I used was of a strength that 1.5 c.c. killed a 500 gram healthy guinea pig within twenty-four to forty-eight hours; I prepared it from cultures of my virulent bacilli. Niemann for his serum, found the relation 7 to 1, while in our case it would be 1 to 1.

But since it was evident that tuberculin did not mean tuberculosis toxin, I worked out another method, which with due regard to the incompleteness of our knowledge gave very satisfactory results.

I profited by Koch's investigations, combining T. O. with T. R. and so getting a fluid which contained, in an absolutely unchanged form, all of the substances (toxins, etc.), the effect of which on the animal organism was to be studied. After the whole of the bacilli had been thoroughly triturated, I gauged the suspensions of them so that every c.c. of the 20 per cent. glycerin solution contained 1 mg. of solid substance. Doses up to 8 and 10 c.c. of this fluid were borne by healthy guinea pigs without any trouble; higher doses produced irregular fever and infiltration; 15 to 16 c.c. invariably caused death.

Quite different was the action on tuberculous animals; 1 mg. always produced, within thirty-six hours, an extended inflammatory infiltration, and a stormy fever reaction differing from the tuberculin reaction

inasmuch as the rise of temperature appears rather sudden (two or three hours after injection) and keeps steady for ten to twelve hours, after which time a decline by lysis occurs. The infiltrations disappear within three days, usually. Very characteristic and interesting is the fact, that in one and the same animal such a reaction may be elicited indefinitely, by only a slight increase of the dosage (Table 15). The common tuberculin reaction, in the same animal, usually fails the third or fourth time. I do not know yet what influence our reaction has upon the tuberculous lesions; existing ulcers heal readily.

If instead of 1 mg. we use 2 mg., this dose invariably produces death within twenty-four hours.

Before we can utilize this toxin for determinations of the antitoxic value of our serum, one objectionable feature of the test will have to be removed, the inequality of the extent of the tuberculous lesions in the animals used. Although in guinea pigs the disease partakes of the character of a self-limited trouble, the extent of the lesions and the constitutional conditions vary enormously in different animals inoculated at the same time. The reactive capacity, naturally, varies with these conditions so that, although for qualitative tests any animal, provided it be tuberculous, will be satisfactory; this is not so for quantitative determinations. Here we must be, as far as possible, sure to always encounter the same power of, or rather lack of power of, resistance in our animals.

The beautiful investigations of Borrel²⁰ and Kaspareck²¹ furnished the material to obviate this difficulty; while the former demonstrated the fact that as soon as thirty-six to forty-eight hours after inoculation, tissue changes became observable, the latter added the valuable information that for the appearance of the tuberculin reaction such tissue changes are necessary, and that this reaction may be typically observed about thirty-eight hours after infection. The eminent theoretic importance of these two facts is apparent (perhaps especially with regard to an alleged pre-tuberculous stage of the disease). I found in them a means to procure for my tests a nearly always equivalent material. If into healthy adult guinea pigs of about the same weight (500 to 700 grams), always the same amount of virus (one loopful of my culture) is injected, and if at a stated interval afterward (forty-eight hours) the same amount of T. O. and T. R. toxin, together with the serum to be tested, is administered, we have done as much as can be done in order to obtain comparable results.

Preliminary experiments showed me that 1 c.c. of my toxin injected into these forty-eight hour guinea pigs elicited the above described reaction, together with a very marked infiltration, while 2 c.c. were here, too, found to be the fatal doses.

By such experiments I knew also that less than 1 c.c. of my serum inhibited all these reactions. If, therefore, we agree to call an antitoxic unit 1 c.c. of that serum which counteracts 1 mg. (1 c.c.) of toxin (always supposed that the serum has been prepared by means of the same race of bacilli from which the toxin is derived), it was easy to determine the potency of the serum under discussion. Accordingly a number of guinea pigs, of about 500 grams weight, were prepared in the way described, whereupon various amounts of serum, each mixed with 1 c.c. of the toxin were injected after forty-eight hours. While .3 c.c. were not able to materially influence the reaction, with .4 c.c. no temperature reaction, nor local infiltration

occurred; .6, .8, and 1 c.c. acted in the same way. This means that the serum is 2.5 times more active than a normal antitoxic serum. In other words, that it represented 2.5 antitoxic units to the c.c. This seems to be a very low value, when compared with the potency of other antitoxic sera. But the serum of the same horse one month later, after immunization had been continued all the time, showed a potency of 3.7. The serum of another horse was found of a strength of 2.8 the first time, of 4.1 six weeks later. These findings I believe to be the most valuable part of my work, since they justify the hope that in due time a serum of very high power may be obtained.

On the other side we must not forget that our serum is not only antitoxic, but in a very high degree also bactericidal, the latter quality being, under certain circumstances, probably more valuable than the former. Furthermore, I think it highly probable that later on a tubercle virus may be obtained of much greater toxicity. Some experiments are under way to find out whether after a method similar to that of Metchnikoff, Roux, and Salimbeni²² (cultivation of tubercle bacilli enclosed in small pouches of collodion which are introduced intraperitoneally into guinea pigs or rabbits), still more virulent forms may be obtained. Be that as it may, my researches so far have demonstrated the fact that a serum both antitoxic and bactericidal may be obtained by immunizing horses against tuberculosis by the new tuberculin T.R., and that it is possible to immunize (and cure) guinea pigs with perfect certainty by means of the serum for which I propose the name "Antiphthisic Serum, T.R."

It would be unnatural not to consider the possibilities that my serum may hold out for the treatment of human tuberculosis, although it is with great reluctance that I venture to make a few remarks on this point. After what has been said in the beginning of this paper, I take the applicability of antitoxin treatment in human tuberculosis for granted. Moreover, the chronic form in which the process usually is met with in man, has certainly to be considered as a favorable point. It can be shown experimentally that the relative toxicity of the watery extracts of finely ground tissues of the organs of tuberculous guinea pigs is enormously higher than that of human tuberculous tissues, in other words, this very chronicity is indicative of a process less productive of toxins. As an admissible objection it might be said that one is not allowed to infer from phenomena observed in one animal, or those observed in another. The more penetrating our investigations become, the more we are forced to admit that the virulence and toxicity of a micro-organism, is by no means the same upon different animals. I think, however, that in the case of the tubercle bacillus, though for obvious reasons a direct proof can not be had, we are perfectly safe in surmising that these differences, if existing at all, are only differences of degree and very slight ones too. In the multifariously confirmed transmissions from animal to man, and *vice versa*, I am inclined to see a confirmation of this surmise.

The antitoxic potency of my serum seems as yet, when compared with other antitoxic sera, to be small, but I do not know whether we have a right to doubt *a priori* its efficacy in man on that account; in the first place, we do not as yet know anything with certainty about the way in which this antitoxic property exerts itself, and whether we are allowed to estimate it quantitatively.²³

But besides this it is a fact that the main toxic action is not exerted by the living bacilli, but by the dead and disintegrating ones, so that a smaller amount of antitoxic power supplied continually will be likely to meet all exigencies. These, however, are problems to be solved in the future. I will only repeat that there seem to be theoretically no limits to the degree of the antitoxic potency, and that practically it is a matter of time and, since T.R. is a rather expensive article, of financial considerations.

The value of T.R. serum for human patients can only be ascertained by a prolonged observation. In about twenty cases so far treated by me and several physicians in and outside of St. Louis, the results have been exceedingly gratifying. I need not tax your patience by telling you what kind of cases we may reasonably expect to be benefited by such treatment. I must lead your attention, however, to the statements of Spengler,²⁴ asserting that a great number of so-called mixed infections are not *a priori* to be considered as hopeless, but that secondary infection very often rapidly subsides and disappears, as soon as some curative influence comes to bear on the tuberculous process.

All of the cases treated, so far as the reports show, were early cases of pulmonary affection; a positive diagnosis was made in every one of them by microscopic examination. In all of these cases, within six to eight weeks a very decided improvement was brought about; temperature became perfectly normal; cough, expectoration, and night sweats stopped; uniformly a considerable increase in weight was observed. The pulse became normal, number of respirations decreased, etc. In all cases, physical examination showed an arrest of the active process, and a clearing up of the affected area; in those cases observed by me the moist râles disappeared within four weeks after treatment began. The latter consisted in daily hypodermic injections of 1 c.c. of the serum. No local or general reaction resulted except now and then a little soreness and swelling around the site of the injection. The most noticeable fact was the lowering of the afternoon temperature, which sometimes would be observed after the first few injections.

I would, however, not like to lay myself open to the reproach of hasty conclusions in a subject the chief element of which is time. A more extensive report will be rendered after the necessary time has elapsed.

The scientific gain of my investigation is the preparation of a really antitoxic and bactericidal antiphthisis serum. With a probability next to a certainty we may expect this serum to become an important factor in the preventive and curative treatment of human tuberculosis; the "importance" of the declining attitude of the Moscow Congress toward serum treatment in tuberculosis will, I am sure, dwindle down to the insignificance and worthlessness inherent to all judgments and criticisms of gregarious masses.

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METRITIS.

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For many years I have been observing in the practice of gynecology a peculiar disease of the uterus characterized by hypertrophy, atrophy or induration. In the chronic state the uterus is hard in consistence. Its walls are rigid and stiff. The disease may occur in a girl of 15 years, or in woman before or after the menopause. It is known as metritis, *i. e.*, an inflammation of the uterine muscularis. I shall attempt to bring forward some views on the disease by the aid of carefully drawn microscopic illustrations. In the

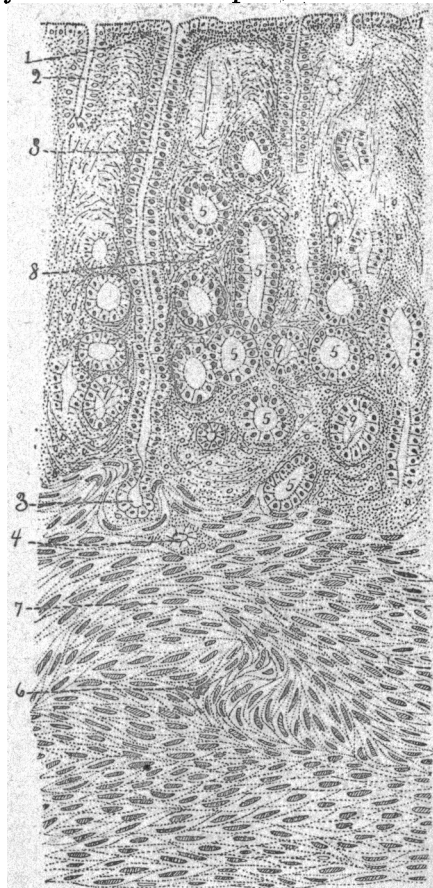


Figure 1 represents a uterus, mucosa and muscularis, in the quiescent stage, in the state of rest, *i. e.*, midway between two menstrual periods. 1, 1, the columnar nucleated, ciliated, single-layered uterine epithelium; 2, a part of a utricular gland opening on the inner surface of the mucosa; 3, a whole utricular gland cut longitudinally, extend-