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Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 13.

M. J. ROSENAU, Director.

May, 1903.

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A STATISTICAL STUDY OF THE INTESTINAL PARASITES  
OF 500 WHITE MALE PATIENTS AT THE UNITED  
STATES GOVERNMENT HOSPITAL FOR THE INSANE.

By PHILIP E. GARRISON, BRAYTON H. RANSOM,  
AND EARLE C. STEVENSON.

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A PARASITIC ROUNDWORM (*Agamomermis culicis* n. g., n. sp.)  
IN AMERICAN MOSQUITOES (*Culex sollicitans*).

By CH. WARDELL STILES.

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THE TYPE SPECIES OF THE CESTODE GENUS *Hymenolepis*.

By CH. WARDELL STILES.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.

1903.

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The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, to be located in Washington, was authorized by act of Congress, March 3, 1901.

The following *bulletins* [Bull. Nos. 1-7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.

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No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Colloidium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

By act of Congress, approved July 1, 1902, the name of the "United States Marine Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.

Since the change of name of the service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:

No. 8.—Laboratory course in bacteriology and pathology. By M. J. Rosenau.

No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.

No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchylostomiasis) in the United States. By Ch. Wardell Stiles.

No. 11.—Experimental investigation of *Trypanosoma Lewisii*. By Edward Francis.

No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.

No. 13.—A statistical study of the intestinal parasites of 500 white male patients of the United States Government Hospital for the Insane; by Philip E. Garrison, Brantton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomernaculicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis*; by Ch. Wardell Stiles.

In citing these bulletins, beginning with No. 8, bibliographers and authors are requested to adopt the following abbreviations: Bull. No. —, Hyg. Lab., U. S. Pub. Health & Mar.-Hosp. Serv., Wash., pp. —.

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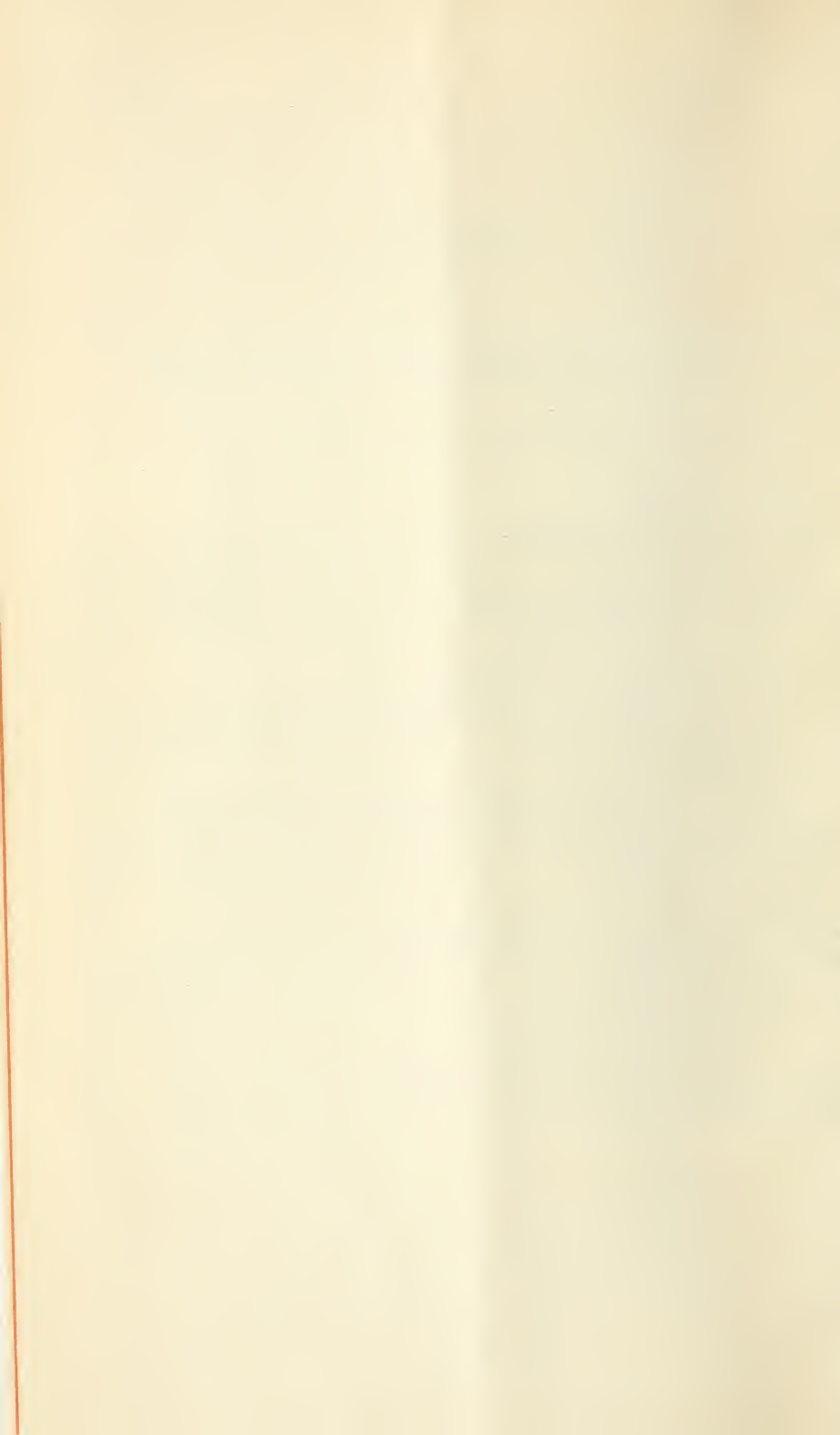


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# A STATISTICAL STUDY OF THE INTESTINAL PARASITES OF 500 WHITE MALE PATIENTS AT THE UNITED STATES GOVERNMENT HOSPITAL FOR THE INSANE.

By PHILIP E. GARRISON, A. B., BRAYTON H. RANSOM, M. A., and EARLE C.  
STEVENSON, B. Sc.,

Assistants in the Division of Zoology, Hygienic Laboratory, U. S. Public Health and  
Marine-Hospital Service.

SUMMARY OF RESULTS.—(1) The results show 13.2 per cent of the patients examined infected with intestinal parasites. The parasites found were hookworms (*Uncinaria americana* or *Agchylostoma duodenale*<sup>a</sup>), whipworms (*Trichuris trichiura*), seatworms (*Oxyuris vermicularis*), Cochin-China worms (*Strongyloides stercoralis*), and eelworms (*Ascaris lumbricoides*). No evidence of infection with tapeworms, flukes, or coccidia was found. (2) Our results differ from those of most foreign investigators principally in the lower rate of infection, in the absence of tapeworms, and in the presence of hookworms and of the Cochin-China worms. (3) The results show that the percentage of infection tends to vary inversely with the age and with the duration of institutional life of the patients. (4) They also indicate that army life is conducive to parasitic infection of the intestine, and, moreover, that a high percentage of the United States soldiers returning from service in the Philippine Islands have intestinal parasites. (5) The presence of a moderate number of worms in the intestine seems to have no relation to the presence of undigested starch and meat in the dejecta or to the litmus reaction of the feces.

INTRODUCTION.—By the courtesy of Dr. A. B. Richardson, superintendent of the Government Hospital for the Insane, a microscopic examination of the feces of the patients in that institution was begun early in

<sup>a</sup> It could not be ascertained with certainty in some cases, from measurement of the ova, that the hookworms belonged to the species *Uncinaria americana*, as the number of the eggs was small and their size somewhat varying. In the great majority of infections, however, the eggs were found to be full 64 by 40  $\mu$  or larger, and we would have little hesitation in calling them *Uncinaria americana* rather than *Agchylostoma duodenale* in every case, were it not for the fact that most of the patients had been in the Philippines, where the Old World form (*Agchylostoma duodenale*) has been found. Final judgment as to the species of the hookworms must be reserved, therefore, until the adult worms can be obtained and examined.

September, 1902, by the Division of Zoology of the Hygienic Laboratory under the direction of Dr. Ch. Wardell Stiles, chief of the Division. The examinations were for the purpose of determining the percentage of intestinal infections with animal parasites and of demonstrating the value of microscopic examination of the feces in general clinical diagnosis. The following results have been obtained from 500 white male patients, and include the number and kinds of infection found with regard to age, length of residence of the patients within the institution, and character of life previous to admission, together with an investigation of the effects of parasitic infection of the intestine upon digestion and upon the litmus reaction of the feces.

FREQUENCY OF INFECTION.—Of the 500 patients examined, 66 patients, or 13.2 per cent, showed parasitic infection of the intestines. Ten patients had a double infection, and in one case three different parasites were present, making a total of 78 infections. These were distributed among five parasites, as follows:

PARASITES PRESENT.—

*Uncinaria americana* or *Ancylostoma duodenale*<sup>a</sup> (hookworms), 15 cases, or 3 per cent of the cases examined.

*Trichuris trichiura* (whipworms), 54 cases, or 10.8 per cent.

*Oxyuris vermicularis* (seatworms), 4 cases, or 0.8 per cent.

*Strongyloides stercoralis* (Cochin-China worms), 3 cases, or 0.6 per cent.

*Ascaris lumbricoides* (eelworms), 2 cases, or 0.4 per cent.

No evidence of parasitic infection of the liver, stomach, lungs, or other organs was present. No tapeworms, flukes, or coccidia were found.

SEVERITY OF INFECTIONS.—In general it may be said that the cases of infection with intestinal parasites found by us at the Government Hospital were not severe. In one or two cases of hookworm disease several eggs were present under a single cover-glass, but in the majority of cases we found only 5 or 6 eggs under the 10 covers examined, and in no case were the ova so numerous as in the severe infections with this parasite found by Dr. Stiles in the Southern States.<sup>b</sup> In some cases of infection with *Trichuris* the eggs were very numerous in the feces and indicated the presence of a great number of worms in the intestine, but as a rule not more than 5 or 6 eggs were found in examining 10 preparations. In one of the infections with *Strongyloides* the feces were rather heavily infested with the embryos. The number of eggs found in the infections with *Oxyuris* and *Ascaris* was small.

<sup>a</sup>See footnote page 5.

<sup>b</sup>Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or ancylostomiasis) in the United States, by Ch. Wardell Stiles, Ph. D., Bull. 10, Hyg. Lab., U. S. Pub. Health & Mar.-Hosp. Serv., Wash., pp. 1-121, figs. 1-86.

The thorough and repeated treatment with purgatives which the patients at the Government Hospital receive may explain the comparatively small number of worms which seem to be present in the infected cases, for in all probability many of the worms are eliminated by repeated purgation.

COMPARISON WITH FOREIGN STATISTICS.—We have at present no American statistics of parasitic infection in adults with which to compare these general results. Following (Table 1) are the tabulated results of similar investigations in Europe and Asia, together with those obtained from the work at the Government Hospital.

TABLE 1.—Statistics of intestinal worms, in United States, Europe, and India.

Authority and locality.	Number of subjects examined.	Hookworms.		<i>Trichuris</i> .		<i>Oxyuris</i> .	
		Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
United States Government Hospital, 1902	500	15	3	54	10.8	4	0.8
Heisig, Germany, 1893	230			104	45.2		
Cima, Italy, 1893, 1896	73			28	38.35	3	4.1
Dobson, India, 1893 <sup>a</sup>	1,249	944	75.58	55	4.41	192	15.37
Kesler, St. Petersburg, 1888	600			30	5	43	7.16
Sievers, Germany, 1887	2,629			521	19.8	326	12.4
Roth, Germany, 1877-1880 <sup>b</sup>	752			178	23.67		
Gribbohm, Germany, 1872-1877 <sup>b</sup>	972			313	32.20	226	23.24
Heller, Kiel, 1872-1875	611			187	30.6	142	23.2
Müller, Germany, 1862-1873 <sup>b</sup>	1,755			159	9.05	213	12.13
Müller, Germany, 1852-1862 <sup>b</sup>	1,989			50	2.57	43	2.21
Zaeslein, Germany <sup>c</sup>					28.7		20
Banik, Germany <sup>c</sup>					8.3		30.6

	<i>Strongyloides</i> .		<i>Ascaris lumbricoides</i> .		<i>Tænia</i> .		Total. <sup>d</sup>	
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
United States Government Hospital, 1902	3	0.6	2	0.4			78	15.6
Heisig, Germany, 1893			34	14.7	2	0.87	140	60.77
Cima, Italy, 1893, 1896			22	30.13	5	6.84	58	79.42
Dobson, India, 1893 <sup>a</sup>			131	10.49	18	1.44	1,340	107.29
Kesler, St. Petersburg, 1888			35	5.83		14.51		
Sievers, Germany, 1887			436	16.56	8	.30	1,291	49.06
Roth, Germany, 1877-1880 <sup>b</sup>			86	11.43			264	35.1
Gribbohm, Germany, 1872-1877 <sup>b</sup>			178	18.30			717	73.76
Heller, Kiel, 1872-1875			108	17.73			437	71.17
Müller, Germany, 1862-1873 <sup>b</sup>			227	12.93			599	34.11
Müller, Germany, 1852-1862 <sup>b</sup>			180	9.28			273	14.07
Zaeslein, Germany <sup>c</sup>				11.4				
Banik, Germany <sup>c</sup>				7.3				

<sup>a</sup>Dobson found also 13 cases of distomatosis (1.04 per cent).

<sup>b</sup>Heisig, 1893. Beitrag zur Statistik menschlicher Entozoen. Greifswald.

<sup>c</sup>Sievers, 1887, Schmarotzer-Statistik aus den Sections-Befunden des pathologischen Instituts zu Kiel.

<sup>d</sup>It will be noted that the figures in the total column represent the number of infections found per 100 cases, not the number of cases infected.

In every case but one the foreign results show a higher percentage of infection with all parasites than was found in our examinations. In no case was mention made of *Strongyloides*, and the only statistics for hookworms are those of Dobson in India, who found there 75.58 per cent of infection with *Agchylostoma duodenale* in examining over 1,200 natives.



AGE.—The average age of the men in whom parasites were found was 37.75 years; of the uninfected cases, 47.9 years. The average age of those infected with hookworms was 32.8 years; with *Trichuris*, 36.1 years; with *Oxyuris*, 66 years; with *Strongyloides*, 45.66 years; with *Ascaris*, 41.5 years.

Dividing the patients into classes according to age, we obtain the following results:

TABLE 2.—Frequency of infection with regard to age of patients.

Age (years).	Number examined.	Hook-worms.		<i>Trichuris</i> .		<i>Oxyuris</i> .		<i>Strongyloides</i> .		<i>Ascaris lumbricoides</i> .		Total. <sup>a</sup>	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
18-30.....	93	7	7.53	17	18.28	0	0	0	0	0	0	24	25.8
31-50.....	184	4	2.17	26	14.13	0	0	2	1.09	2	1.09	34	18.42
51+.....	194	1	0.52	5	2.53	4	2.01	1	0.52	0	0	11	5.67
Unknown.....	29	3	10.34	6	20.69	0	0	0	0	0	0	9	31.03
Total.....	500	15	3.00	54	10.8	4	0.8	3	0.6	2	0.4	78	15.6

<sup>a</sup> See footnote *d*, table 1.

The rate of infection decreases as the age of the patients increases. Heisig found similar results in Germany, though his percentages were higher and his patients included both men and women.

TABLE 3.

	15 (18)-30 years.			31-50 years.			51+ years.		
	Number examined.	Infected.		Number examined.	Infected.		Number examined.	Infected.	
		No.	Per cent.		No.	Per cent.		No.	Per cent.
Heisig.....	17	7	41.5	28	9	32.1	23	8	13.
Government hospital.	93	24	25.8	184	33	17.9	194	11	5.67

LENGTH OF RESIDENCE IN THE HOSPITAL.—Considering the amount of infection found with regard to the length of residence of the patients within the hospital, the results are as follows: Admitted within one year, 162 men; infected, 28 men, or 17.28 per cent. With from one to three years' residence, 154 men; infected, 20, or 12.99 per cent. From three to eight years, 57 men; infected, 5, or 8.77 per cent. From eight to fifteen years, 45 men; infected, 3, or 6.66 per cent. More than fifteen years, 71 men; infected, 7, or 9.86 per cent.

The rate of infection decreases as the length of residence in the hospital increases, except in the class which had spent fifteen years or more in the institution, where the percentage rises.

The following table gives the frequency of infection with each parasite in each of the above classes:

TABLE 4.—*Frequency of infection with regard to length of residence in the hospital.*

Number of years.	Number examined.	Hook-worms.		<i>Trichuris.</i>		<i>Oxyuris.</i>		<i>Strongyloides.</i>		<i>Ascaris lumbricoides.</i>		Total. <sup>a</sup>	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
-1.....	162	9	5.5	26	16.09	0	0	0	0	1	0.62	36	22.22
1-3.....	154	4	2.57	18	11.69	0	0	3	1.95	0	0	25	16.23
4-8.....	57	1	1.75	5	8.77	0	0	0	0	1	1.75	7	12.28
9-15.....	45	1	2.22	1	2.22	1	2.22	0	0	0	0	3	6.66
15+.....	71	0	0	4	5.63	3	4.23	0	0	0	0	7	9.86
No record.....	11	0	0	0	0	0	0	0	0	0	0	0	0
Total.....	500	15	3.00	54	10.8	4	0.8	3	0.6	2	0.4	78	15.6

<sup>a</sup> See footnote *d*, table 1.

CHARACTER OF LIFE PREVIOUS TO ADMISSION.—Considering the patients examined with regard to the character and conditions of their life immediately previous to admission to the hospital, they fall into four main groups—those admitted from the Army, those admitted from the United States Soldiers' Homes, those admitted from the District of Columbia, and those admitted from the Navy. A fifth or miscellaneous class contains a small number of United States convicts, patients admitted from the United States Territories, and a few men concerning whose previous life no data were obtainable. The Army group is naturally subdivided into three classes: First, men admitted before the outbreak of the Spanish-American war (1898), composed of soldiers from the regular army posts; second, soldiers engaged in that war who served within the States; and, a third and important class, soldiers who had returned from service in the Philippine Islands.<sup>a</sup>

*Soldiers admitted before 1898.*—This class included 30 men, 4 of whom, or 10 per cent, had intestinal parasites. Three infections were with *Trichuris trichiura* and 1 with *Oxyuris vermicularis*.

*Soldiers admitted after 1898.*—This class also contained 40 men, 9 of whom, or 22.5 per cent, were infected with parasites. Eight infections were with *Trichuris trichiura* and 1 with hookworms.

*Soldiers returned from the Philippines.*—Fifty-nine men were examined who had returned from service in the Philippines. Twenty-five of these, or 42.46 per cent, had intestinal parasites. Fifteen men were infected with *Trichuris* alone, 1 with hookworms alone, 7 with hookworms and *Trichuris*, 1 with hookworms and *Strongyloides*, and 1 with hookworms, *Trichuris*, and *Ascaris*. Thus in the 59 soldiers

<sup>a</sup> Of the soldiers admitted to the Government hospital after service in Cuba and Porto Rico nearly all had been discharged before these investigations were begun, so that the interesting statistics which might be expected from this class were not obtainable.

there were 10 infections with hookworms, 23 infections with *Trichuris*, 1 infection with *Strongyloides*, and 1 infection with *Ascaris*, or a total of 35 infections.

*Men admitted from the United States Soldiers' Homes.*—Of the 124 men admitted from the United States Soldiers' Homes 8 men, or 6.45 per cent, were infected. Hookworms, *Oxyuris*, *Strongyloides*, and *Ascaris* were each found once, while *Trichuris* was present four times.

*Men admitted from the District of Columbia.*—This class included 137 men, 11 of whom, or 8.03 per cent, were infected, namely, 9 with *Trichuris*, 1 with *Oxyuris*, and 1 with *Strongyloides*.

*Men admitted from the Navy.*—Forty-two patients were admitted from the Navy or from naval hospitals. Of this number 4 men, or 9.5 per cent, had intestinal parasites. Hookworms were found once and *Trichuris* was found three times.

*Miscellaneous.*—Of the 58 patients not classified, 7 men, or 12.07 per cent, showed infection, namely, 2 with hookworms, 4 with *Trichuris*, and 1 with *Oxyuris*.

These results are summarized in the following table:

TABLE 5.—Frequency of infection with regard to character of life previous to admission to the hospital.

Previous history.	No. examined.	Hookworms.		<i>Trichuris</i> .		<i>Oxyuris</i> .		<i>Strongyloides</i> .		<i>Ascaris lumbricoides</i> .		Total. <sup>a</sup>	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Army before 1898.....	40	0	0	3	7.5	1	2.5	0	0	0	0	4	10.0
Army after 1898.....	40	1	2.5	8	20.0	0	0	0	0	0	0	9	22.5
Philippine Islands.....	59	10	16.95	23	38.98	0	0	1	1.7	1	1.7	35	59.32
Soldiers' Homes.....	124	1	0.81	4	3.23	1	0.81	1	0.81	1	0.81	8	6.45
District of Columbia.....	137	0	0	9	6.57	1	0.73	1	0.73	0	0	11	8.03
Navy.....	42	1	2.38	3	7.14	0	0	0	0	0	0	4	9.52
Others.....	58	2	3.47	4	6.9	1	1.72	0	0	0	0	7	12.09
Total.....	500	15	3.00	54	10.8	4	0.8	3	0.6	2	0.4	78	15.6

<sup>a</sup> See footnote *a*, Table 1.

THE SIGNIFICANCE OF AGE, INSTITUTIONAL LIFE, AND THE CONDITIONS OF PREVIOUS LIFE WITH REGARD TO THE AMOUNT OF INFECTION WITH INTESTINAL PARASITES.—The soldiers admitted after service in the Philippine Islands, among whom was found a percentage of infection more than twice as high as in any other class, were for the most part young men, their average age being 30.5 years. They were also patients of recent admission, none having been in the hospital longer than three years. We may discover the relative significance of Philippine service as a condition favorable to infection with intestinal parasites by comparing the Philippine men with that class of patients who during the late war served in the reserve camps situated principally in the Southern States. The average age of this latter class of men was 34.8 years, and all but four had been admitted to the hospital



within three years, thus presenting conditions about the same as found among the Philippine men. The frequency of infection, however, was only 20 per cent, as compared with 42.46 per cent among the soldiers returned from the Philippine Islands. The much higher rate of infection in the Philippine men can be accounted for by the greater prevalence of the parasites in the Philippines and by the poor sanitary conditions under which it was necessary for the men to live during active service in the islands.

The results obtained in these examinations at the Government hospital would indicate that a large number of the United States soldiers returning from service in the Philippine Islands return with a parasitic infection of the intestines. While the percentage of infection with hookworms (16.95 per cent) among these soldiers was not so high as that with whipworms (39.98 per cent), its clinical importance is much greater, because of the severe anemic and nervous symptoms which the hookworm is capable of producing; and the danger of this parasite being spread in this country, especially the danger of its being carried to parts of the country where it does not now exist, makes the presence of hookworm infection among the soldiers returning from the Philippines a matter of moment from the view-point of public health.<sup>a</sup>

The patients admitted from the Army after the outbreak of the Spanish-American war show a much higher rate of infection (20 per cent) than do those admitted from the Regular Army before 1898 (10 per cent). In the former class we find an average age of 34.8 years and only four men who had been in the hospital longer than three years. In the latter class the average age was 45.6 years, and all except six of the men had been in the hospital longer than eight years. Accordingly, the lower percentage of infection among the soldiers admitted before the war seems to be due to a combination of three factors, namely, greater age, longer period of institutional life, and the better sanitary and hygienic conditions found at the Regular Army posts than in the temporary reserve camps established during the war.

Considering the 124 patients who had been admitted to the Government hospital from the United States Soldiers' Homes, we find the highest average age (62.9 years) of any of the classes studied, and while 97 of the 124 men had been received at the hospital within three years prior to our examination, all of them had resided for a longer or shorter period at the Soldiers' Homes, so that we have a combina-

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<sup>a</sup>Since this report was prepared the feces of 9 soldiers newly arrived at the Government hospital from the Philippines have been examined for parasites. Six of the 9 men were infected, 1 with hookworms alone, 1 with hookworms and *Trichuris*, 2 with *Trichuris* alone, 1 with *Ascaris lumbricoides* alone, and 1 with *Ascaris lumbricoides* and *Trichuris*.

tion of old age and a long period of institutional life. In this class we found the lowest rate of infection (6.45 per cent).

The 137 civilians admitted to the hospital from the District of Columbia were rather evenly distributed both with regard to age and to length of residence in the institution. Their average age was 42.5 years. Seventy-four men had been admitted within four years, and 59 had had longer than four years' residence in the hospital. Of the 137 men 8.03 per cent were found infected. The 74 patients who had been admitted within four years showed 9.46 per cent of infection, while the 59 patients with a longer residence showed only 6.78 per cent.

These results are lower than those obtained by Sommer in the District of Columbia in 1895. (Southern Journal of Homœopathy, December, 1895, pp. 353-354.) In examining 36 children, ranging from 1 month to 14 years in age, in the Children's Hospital of the District, he found 11.11 per cent to have intestinal parasites. All the infections were with *Trichuris*. The difference in age and in condition between his patients and those examined at the Government hospital may well explain the disparity in results.

In the 42 patients admitted from the United States Navy we find again a younger class of men, averaging 34.6 years, and men of comparatively recent admission to the hospital, 25 of the 42 having been received within three years prior to our examination. Although the average age and the average length of institutional life are lower in this class than in the soldiers admitted from the Regular Army, the percentage of infection is lower, for which we must hold accountable the conditions of their life prior to admission.

**DIGESTION.**—In the investigation of the relation of parasitic infection of the intestines to the presence of undigested food in the feces our results were entirely negative. In 28 cases large quantities of undigested starch granules were found in the stools and in 7 cases a large quantity of undigested meat fibers. Of these 35 cases only 6 were infected with parasites. On the other hand there were 61 men with parasites present in the intestine who did not show this evidence of poor digestion of starch or meat.

**LITMUS REACTION OF FECES.**—The litmus test was made of the feces of 324 patients. Of the 270 uninfected cases tested 79.26 per cent were alkaline, 15.93 per cent acid, and 4.81 per cent gave no reaction. Of 54 cases tested where parasites were present 81.48 per cent were alkaline, 12.77 per cent acid, and 5.55 per cent gave no reaction. About the same results were obtained by considering the infections with each parasite separately, alkaline and acid reaction being present in practically the same proportions as in the uninfected feces. The results, therefore, must be considered as entirely negative.

**TECHNIQUE.**—Some difficulty was anticipated in obtaining the fecal specimens and in conveying them from the hospital into the city to

the laboratory, where the examinations were to be made, but as the work progressed the following methods were developed and very little trouble was experienced:

The attendants on the wards were provided with aluminum chambers into which the stools were passed in the morning before or immediately after breakfast, when the patients generally desire to defecate. The stubbornness and the suspicious ideas of the patients in many cases were difficult to overcome, but there were very few cases where by patience and persistence on the part of the attendants the specimen could not be obtained. The chambers containing the feces were set aside in a vacant room by the attendants.

From one to two grams was taken from each specimen (preferably from the surface) and wrapped in a piece of common wrapping paper. These papers being thoroughly wrapped together in a large piece of paper made a small package which could be carried handily and without odor. In case the excrement were fluid, small glass jars with screw tops were used. To transfer the specimen to the paper or jar we made use of 1 by 3 inch glass slides, which were cleanly and could be readily washed and reused, or of stiff cardboard slips.

Ten preparations were made from each specimen for examination with the microscope, using the following technique: The large 2 by 3 inch glass slides were used, these being cleaner and more easily handled than the ordinary 1 by 3 inch slide. A drop of distilled water was placed on each slide, and with this a portion of the feces little larger than a pin head was thoroughly mixed by rubbing with the end of a glass rod. On this preparation was placed a three-quarter inch cover glass (square preferred) of medium thickness. Two preparations were made on each slide and then examined with the microscope while fresh without staining, using a lens of moderate power, such as the Zeiss 8 mm. or the Zeiss C. To insure greater accuracy at least two men examined preparations from each specimen. The examination of ten specimens (100 preparations) is an average day's work for one person.





# A PARASITIC ROUNDWORM (AGAMOMERMIS CULICIS N. G., N. SP.) IN AMERICAN MOSQUITOES (CULEX SOLLICITANS).

By CH. WARDELL STILES, Ph. D.

Chief of Division of Zoology, Hygienic Laboratory, United States Public Health and Marine-Hospital Service.

At a time when mosquitoes are subjected to such careful study, because of the important relations they bear to public health, especially in connection with malaria, yellow fever, etc., it is of interest to determine what parasites naturally infest them. This determination has its practical as well as its scientific value, for it enables us to eliminate certain nonpathogenic parasitic organisms from the life cycle of pathogenic organisms, stages of which may be found in mosquitoes. It further has its direct practical bearing in that the parasites of mosquitoes may multiply to such an extent as to become important factors in killing the insects, or at least in rendering them less fertile.

Quite recently several parasites have been described for the Culicidæ. Ross (1895) has found intestinal gregarines in mosquito larvæ in India. Perroncito (1899) has found a filamentous phytoparasite in *Anopheles* collected near Turin, Italy. Laveran (1902) has described a pathogenic yeast in the abdominal cavity of *Anopheles maculipennis* collected in Spain, and he reports various acarines as external parasites of the Culicidæ. Léger (1902) has described a parasitic flagellate (*Crithidia fasciculata*) in the intestine of the adult female of *Anopheles maculipennis*. Herbert Johnson (1902) has described a sporozoon as infecting about 8 per cent of the females of *Anopheles maculipennis* collected in a certain locality in Massachusetts in which tertian malaria is endemic. Martirano (1901) has described a minute trematode (*Agamodistomum Martiranoi*<sup>a</sup> Stiles, 1903 [new name]) found in the body cavity of *Anopheles claviger* (= *A. maculipennis*) taken in Italy. G. W. Mueller found an undetermined sporozoon of the genus *Glugea* in *Culex*.

To these cases of parasitism I am now able to add another of considerable interest. Prof. John B. Smith, of Rutgers College, has

<sup>a</sup>Martirano, 1901, Centralbl. f. Bakteriol., Parasitenk. [etc.], Jena, v. 30 (23), 24. Dec., pp. 849-852, figs. 1-4.

kindly forwarded to me for examination two worms taken from the abdominal cavity of *Culex sollicitans*. One specimen was hardly in condition to be of use in study, but it represented a larval roundworm, probably either a *Mermis* or a *Paramermis*. The second specimen was determined as a larval roundworm, but owing to the fact that its genital organs were not developed, its exact generic position could not be recognized. It apparently belongs in the family Mermithidæ, either to *Mermis* or to *Paramermis*. It will be convenient to recognize for these larval forms a special biological group, for which I propose the name *Agamomermis*.

The characters of the groups in question may be summarized as follows:

### Family MERMITHIDÆ.

FAMILY DIAGNOSIS.—Thread-like worms, quite similar to *Filaria* in general appearance. Mouth with 6 papillæ. In adults, the posterior end of the intestinal canal is more or less atrophied. Male with 1 or 2 spicules and with numerous caudal papillæ arranged in three or four rows. Larvæ parasitic, especially in the abdominal cavity of arthropods; adults free living.

TYPE GENUS.—*Mermis* Dujardin, 1842.

#### Genus MERMIS Dujardin, 1842.

GENERIC DIAGNOSIS.—Mermithidæ: Male with two equal spicules.

TYPE SPECIES.—*Mermis nigrescens* Dujardin, 1842.

#### Genus PARAMERMIS von Linstow, 1898.

GENERIC DIAGNOSIS.—Mermithidæ: Male with one spicule.

TYPE SPECIES.—Not determined—either *P. crassa* (von Linstow, 1889) or *P. aquatilis* (Dujardin, 1845).

#### Group AGAMOMERMIS Stiles, 1903.

GENERIC DIAGNOSIS.—Mermithidæ: An artificial collective group containing larval forms which can not be more definitely determined because of lack of genital organs. As such a group is artificial it should have no type species.

#### Species AGAMOMERMIS CULICIS Stiles, 1903.

SPECIFIC DIAGNOSIS.—*Agamomermis*: About 11 mm. long; 240  $\mu$  in diameter. Caudal spine 88  $\mu$  long.

HABITAT.—Abdominal cavity of mosquitoes (*Culex sollicitans*), New Jersey.

TYPE SPECIMEN.—Collection U. S. P. H. & M.-H. S., No. 9401,<sup>a</sup> in poor condition; collected by Dr. John B. Smith, New Brunswick, N. J.

<sup>a</sup> IMPORTANT NOTICE TO HELMINTHOLOGISTS.—In order to prevent confusion, and following the precedent of the United States Bureau of Animal Industry, the specimens of parasites and of other objects in medical zoology which become property of the Division of Zoology, Hygienic Laboratory, United States Public Health and Marine-Hospital Service, will be given numbers in the series of the Helminthological Collection of the United States National Museum.

Nos. 1 to 4700 have been set aside for the United States Bureau of Animal Industry.

Nos. 4701 to 9400 have been set aside for the miscellaneous specimens of parasites deposited in or presented to the United States National Museum or sent to the Museum for determination.

Nos. 9401 to — have been set aside for the United States Public Health and Marine-Hospital Service.

In the summer of 1889 I collected a number of specimens of *Agamomermis* sp. from mosquitoes of the species *Culex nemoralis* taken in the vicinity of Leipzig, Saxony. Whether they were identical with the present form I am unable to state. The interesting fact may be mentioned, however, that the Leipzig *Agamomermis* was decidedly injurious to the mosquitoes. It was found in the abdominal cavity of larvæ, pupæ, and adults, so that infection must have taken place in the water, namely, in the larval and pupal stages of the *Culex*. The infested insects were very sluggish in their movements and could usually be easily recognized as diseased. Many of them died from the effects of the parasite, and the ovaries of infected females were underdeveloped. Professor Leuckart informed me at that time that he had frequently found *Culex nemoralis* infected with this worm, and that during the years that the worms were most common the mosquitoes seemed to be less numerous.

These cases represent interesting instances in nature, where a pest is subject to other pests which tend to hold the former in check.

At least two other species of *Mermis* should be placed in the collective group *Agamomermis*, namely, *Agamomermis gammari* (von Linstow, 1892), parasitic in *Gammarus pulex*, and *A. sialidis* (von Linstow, 1892), parasitic in *Sialis lutaria*.

*Bibliography.*—Bibliographic citations follow the references in Stiles & Hassall, Index-Catalogue of Medical and Veterinary Zoology, Bull. 39, Bureau Animal Industry, U. S. Dept. Agric., Wash.





## THE TYPE SPECIES OF THE CESTODE GENUS HYMENOLEPIS.

By CH. WARDELL STILES, Ph. D.,

Chief of Division of Zoology, Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service.

The determination of type species for certain genera is not unattended with difficulties and with differences of opinion. *Hymenolepis*, for example, presents an instance in regard to which helminthologists are not in accord. The premises of the case are these:

(1) Weinland (1858, § 68, pp. 49 to 57) proposed the genus *Hymenolepis*. (2) He did not specifically state that any particular species was chosen as a type; (3) but he combined only one specific name, namely, *flavopunctata* (= *Tænia diminuta*), with *Hymenolepis* (see Weinland, 1858, pp. x, 16, 49, 52, 53, 55, 57, 58, 75, 85, 92). (4) His discussion of the genus is based on this form. (5) In a footnote, pp. 50 to 53, to this discussion, he reviews the classification of certain tapeworms and, p. 52, he mentions *Hymenolepis*. (6) This genus he there divides into two subgenera, namely, (7) Subgenus 1. *Lepidotrias*, stating "As the type, we may consider *Tænia murina* Dujardin; and besides this belong here *Tænia scalaris*, -----, and *Hymenolepis flavopunctata*." (8) Subgenus 2. *Dilepis* -----, "and we may consider *Tænia angulata* Rudolphi as its type." (9) In *Dilepis* he also placed, besides other species, "the Tænioid of the golden-winged woodpecker, mentioned above, § 28." (10) The latter form is evidently *Liga punctata*, described in 1857 as new species from *Picus auratus* (= the flicker, *Colaptes auratus* (Linnaeus, 1758), Vigors, 1827), as is seen from the description of the testicles. (11) *Liga punctata* is type and only species of *Liga* Weinland, 1857.

In this case, therefore, at the date of 1858 we have four generic names (*Hymenolepis*, 1858; *Lepidotrias*, 1858; *Dilepis*, 1858; and *Liga*, 1857) to deal with, and of these Weinland should undoubtedly have used *Liga* instead of proposing *Hymenolepis*.

Types were definitely fixed for *Lepidotrias*, namely, *Tænia murina* Dujardin, 1845 (not Gmelin, 1789) = *Tænia nana* von Siebold, 1852, which is also type of *Diplacanthus* Weinland, 1858 (not Agassiz, 1842); for *Dilepis*, namely, *T. angulata*; and for *Liga*, namely, *L. punctata*.

As the subgenus *Dilepis*, 1858, contained the older genus *Liga*, 1857, Weinland should not have proposed *Dilepis*; but since he definitely

proposed *T. angulata* as type, the case comes under § 7 of the Stricklandian code, which states: "Provided, however, that if these authors select their respective types from different sections of the genus, and these sections be afterward raised into separate genera, then these names may be retained in a restricted sense for the new genera, respectively." Thus as long as *Liga* and *Dilepis* are considered generically or subgenerically identical, *Liga*, 1857, takes precedence over *Dilepis*, 1858; but if *Liga* and *Dilepis* are recognized as generically distinct, both names are available (but not necessarily valid) for the respective genera or subgenera.

In determining the type of *Hymenolepis* we have before us a case of practically the same nature. Weinland has definitely designated *Tænia murina* as type of *Lepidotrias*, but he has placed *Hymenolepis flavopunctata* in this subgenus. The genus *Hymenolepis* itself is based directly upon *flavopunctata*, as is clearly shown by the reference, "Gen. 1. *Hymenolepis* Weinland (see § 68)," for § 68 is the discussion of *H. flavopunctata*, and this reference "(see § 68)" can, and I believe it should, be interpreted as designation of the type. Thus, if *Hymenolepis flavopunctata* (= *T. diminuta*) and *Tænia murina* (= *T. nana*) are congeneric, *Lepidotrias* is synonym of *Hymenolepis*; but should these two species ever be recognized as generically distinct, both names are available in determining the valid names of the respective genera.

In 1896 I published *flavopunctata*=*diminuta* as type of *Hymenolepis*, basing my action on the above interpretation, but not publishing the details.

At that time the fact had escaped my attention that Blanchard (1891a) had mentioned *T. murina*=*T. nana* as type. Blanchard's reasoning was apparently based on the view that *Hymenolepis* had been divided into two subgenera, both of the latter having type species; hence either *murina* or *angulata* should be type of *Hymenolepis*.

There is a certain amount of justice in this point of view, and it must be admitted that one of Weinland's (1861, pp. 1-24) papers lends considerable support to it. Still this interpretation does not appear to correspond altogether with Weinland's earlier publications or intentions. In chronological sequence Weinland's text (§ 68) was surely written before his footnote. The fact that he consistently combined *flavopunctata*, but no other species, with *Hymenolepis* is significant. Further, if *flavopunctata* is taken as type of *Hymenolepis*, the name *Lepidotrias* is not hopelessly suppressed, while if *murina*=*nana* is taken as type of *Hymenolepis* we needlessly forfeit all use of *Lepidotrias* unless *Hymenolepis* should eventually prove to be a homonym.

In order to obtain the views of other zoologists who have made a special study of the principles involved in determining type species, I have laid this case, with the original literature in question, before Drs. Merriam and Palmer (mammalogists and ornithologists), Dr. Stejneger

(ornithologist and herpetologist), Dr. Gill (ichthyologist), Dr. Dall, (conchologist), and Dr. Benedict and Miss Rathbun (both of whom have given especial attention to the types of crustacea). Of these 7 specialists, none of whom knew which position Blanchard supported and which one I adopted, Dr. Palmer inclined to the view that *murina* (= *nana*) should be the type of *Hymenolepis*; Dr. Benedict thought that it might be either *murina* or *flavopunctata*, and all the other 5 thought that no question could be raised since it seemed so evident that Weinland himself looked upon *flavopunctata* as type of *Hymenolepis*.

Braun (1900a, pp. 1669, 1717) accepts *Tænia diminuta* as type of *Hymenolepis*, thus adopting the ruling I made in 1896.

*Bibliography.*—Bibliographic citations follow the references in Stiles & Hassall, Index-Catalogue of Medical and Veterinary Zoology, Bull. 39, Bureau Animal Industry, U. S. Dept. Agric., Wash.



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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 14.

M. J. ROSENAU, Director,

July, 1903.

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# SPOTTED FEVER (TICK FEVER) OF THE ROCKY MOUNTAINS.

---

*A NEW DISEASE.*

---

By JOHN F. ANDERSON.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.

1903.



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The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, to be located in Washington, was authorized by act of Congress, March 3, 1901.

The following *bulletins* [Bulls. Nos. 1-7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

- No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.
- No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.
- No. 3.—Sulphur dioxide as a germicidal agent. By H. D. Geddings.
- No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.
- No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.
- No. 6.—Disinfection against mosquitoes with formaldehyd and sulphur dioxide. By M. J. Rosenau.
- No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

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- No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchylostomiasis) in the United States. By Ch. Wardell Stiles.
- No. 11.—Experimental investigation of *Trypanosoma Lewisi*. By Edward Francis.
- No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.
- No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis*; by Ch. Wardell Stiles.
- No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.

In citing these bulletins, beginning with No. 8, bibliographers and authors are requested to adopt the following abbreviations: Bull. No. —, Hyg. Lab., U. S. Pub. Health & Mar.-Hosp. Serv., Wash., pp. —.

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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

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WALTER WYMAN, *Surgeon-General.*  
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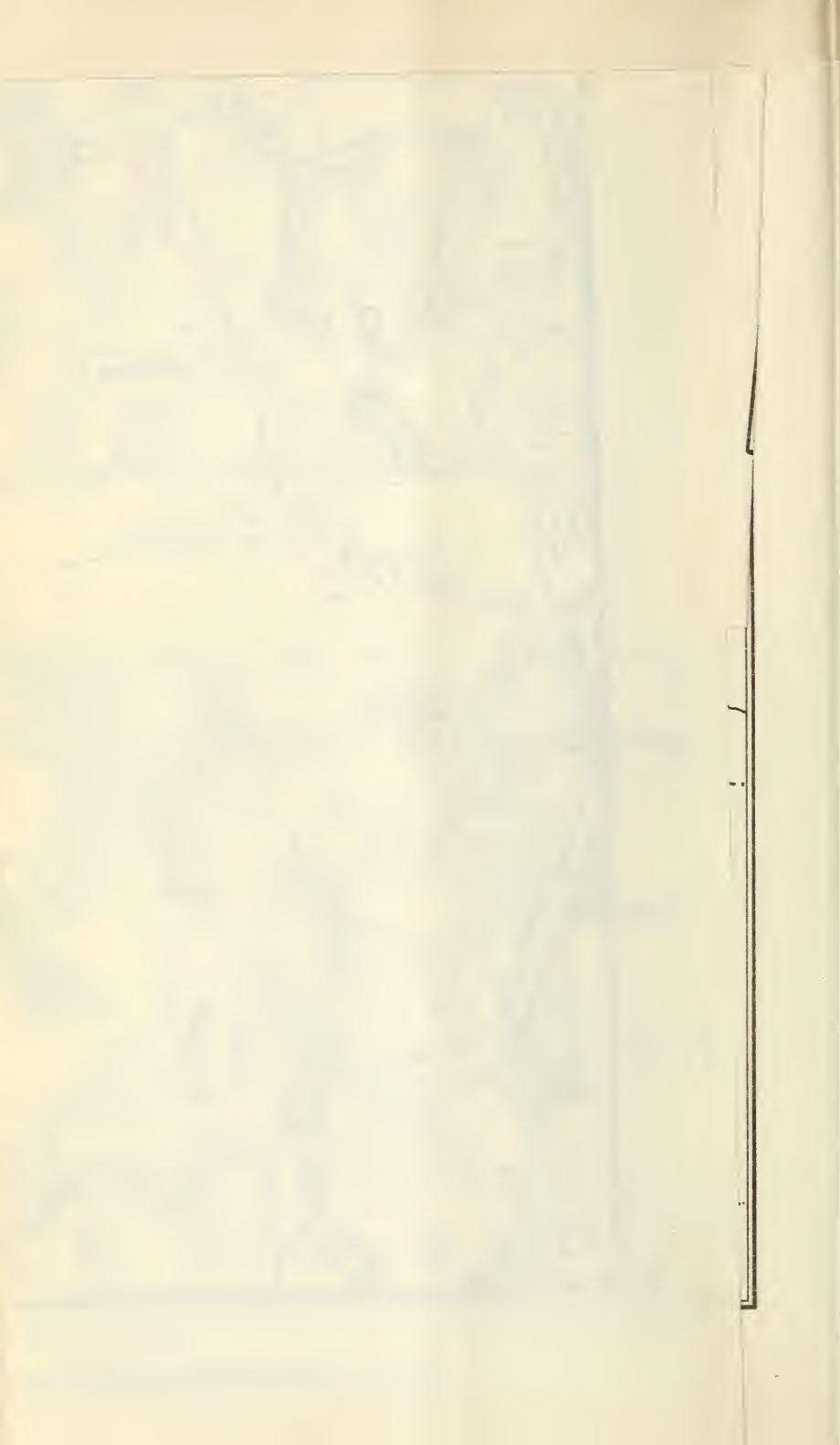
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# SPOTTED FEVER (TICK FEVER) OF THE ROCKY MOUNTAINS; A NEW DISEASE.

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## INTRODUCTION.

In obedience to instructions of April 22, 1903, to proceed to Montana to investigate the so-called spotted fever which has prevailed at times in the Bitter Root Valley, I left Washington April 24.

I first visited Great Falls, Mont., for the purpose of conferring with Dr. A. F. Longeway, secretary of the Montana State Board of Health; from there I went to Missoula, situated at the foot of the Bitter Root Valley, and made that place my headquarters. The Montana State University very courteously offered me the use of its laboratory. Dr. J. J. Buckley, chief surgeon of the Northern Pacific Railroad, also offered me the use of his laboratory, which was accepted.

As is shown in the report, the disease is not confined to the Bitter Root Valley, but exists in Nevada and Idaho; and since writing my report I have been informed of cases in Wyoming.

The good results that have followed the administration of large doses of quinine—the five cases in which it was used having recovered—give much hope that this disease, which is so much dreaded, may in the future be robbed of many of its terrors.

I have suggested as a name for the disease "Tick Fever," as there are already two diseases sometimes called "spotted fever."

I desire to express to Dr. J. J. Buckley, of Missoula, for the use of his laboratory, and to the physicians of Missoula and the Bitter Root Valley, my sincerest thanks for their kind assistance in my investigation of the disease and for many personal courtesies; also, to Dr. L. B. Wilson, of the University of Minnesota, for help and data in regard to the disease.

To Surg. Gen. Walter Wyman I am much indebted for the detail and resulting opportunity to study this new and most interesting disease.



SCALE: 1 INCH=115 MILES.

MAP SHOWING THE LOCATION OF REPORTED CASES OF SPOTTED FEVER.



## ETIOLOGY.

## 1. GEOGRAPHIC DISTRIBUTION.

*Montana.*—The disease has been known in the valley of the Bitter Root River in western Montana for about twenty years. It is sharply localized on the west bank of the Bitter Root River, no cases having been known to occur in persons on the east side of the river who had not a short time previously visited the west side. The infected locality extends from Loo Loo to Como, a distance of about 50 miles. Certain places in the valley seem to be more heavily infected than others. Nine cases have also occurred in the canyon of Rock Creek, about 10 miles south of Bonito and 20 miles east of the Bitter Root.

This year information was obtained from Dr. L. A. Gates, of Bridger, Mont., about 400 miles east of the Bitter Root, of the prevalence of the disease in that locality. A report of two cases described by him will be seen in the appendix.

*Idaho.*—The disease has also been known clinically in Idaho for many years, the first published description having been made by Dr. E. E. Maxey, in the Portland Medical Sentinel for October, 1899 (1). An unpublished symposium on the disease by various Idaho physicians was made by Maj. M. W. Wood, U. S. Army, 1898, to the Surgeon-General of the Army. In Idaho the disease prevails throughout almost the entire valley of the Snake River, its tributaries, and the foothills of the neighboring mountains.

*Nevada.*—I am informed by Maj. W. R. Kendall, U. S. Army, that the disease also prevails in the valley of the Quinn River in northern Nevada.

*Wyoming.*—Cases have been reported this spring at Cody and Meeteetse.

*Oregon.*—The mild form of the disease has been reported in eastern Oregon.

## 2. CLIMATE.

The disease does not prevail south of 40° or north of 47°. It prevails at an average elevation of about 3,000 to 4,000 feet above sea level.

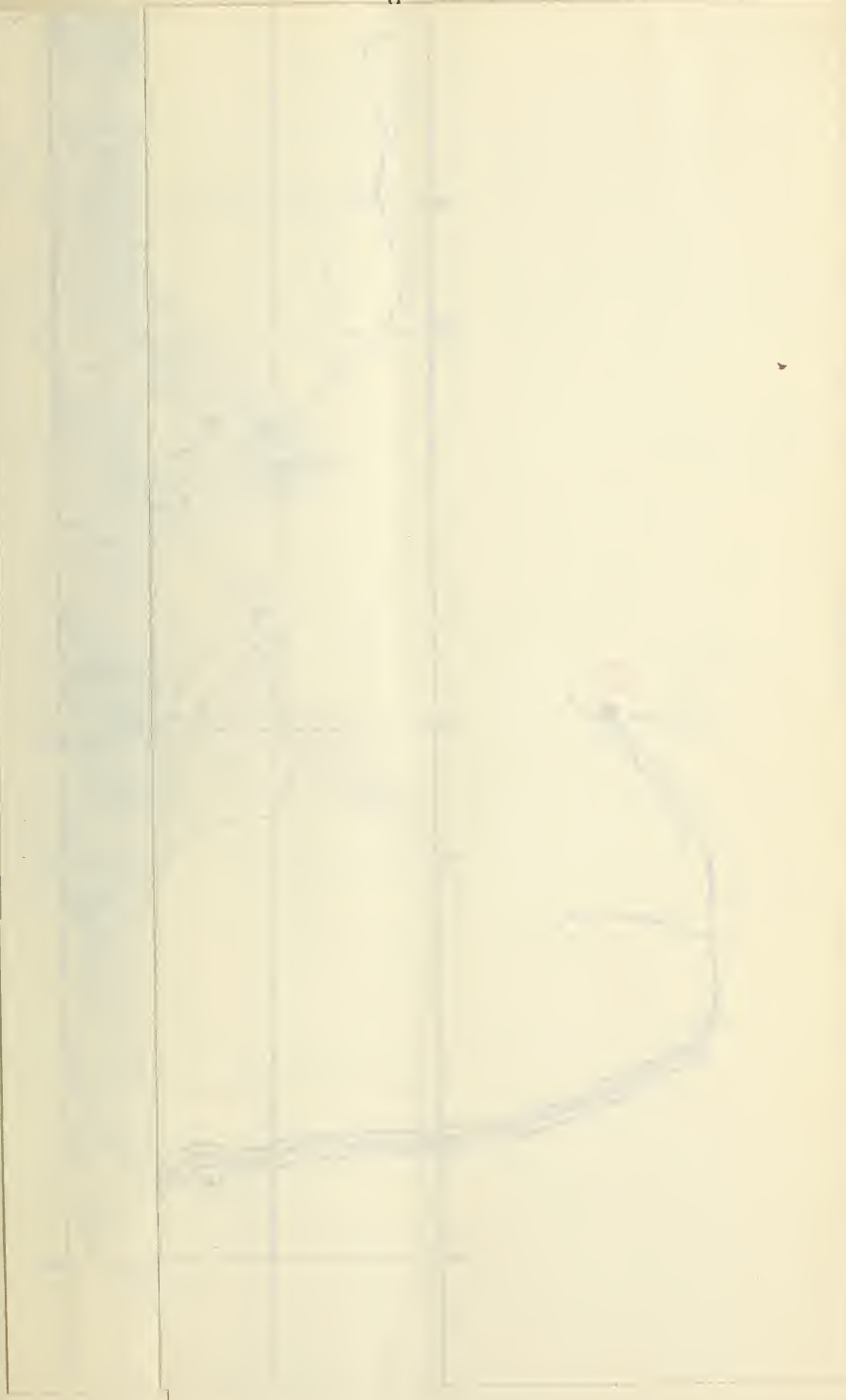
## 3. SEASON.

The disease prevails exclusively in the spring and early summer. In the Bitter Root cases the earliest was March 17 and the latest July 20.

## 4. OCCUPATION.

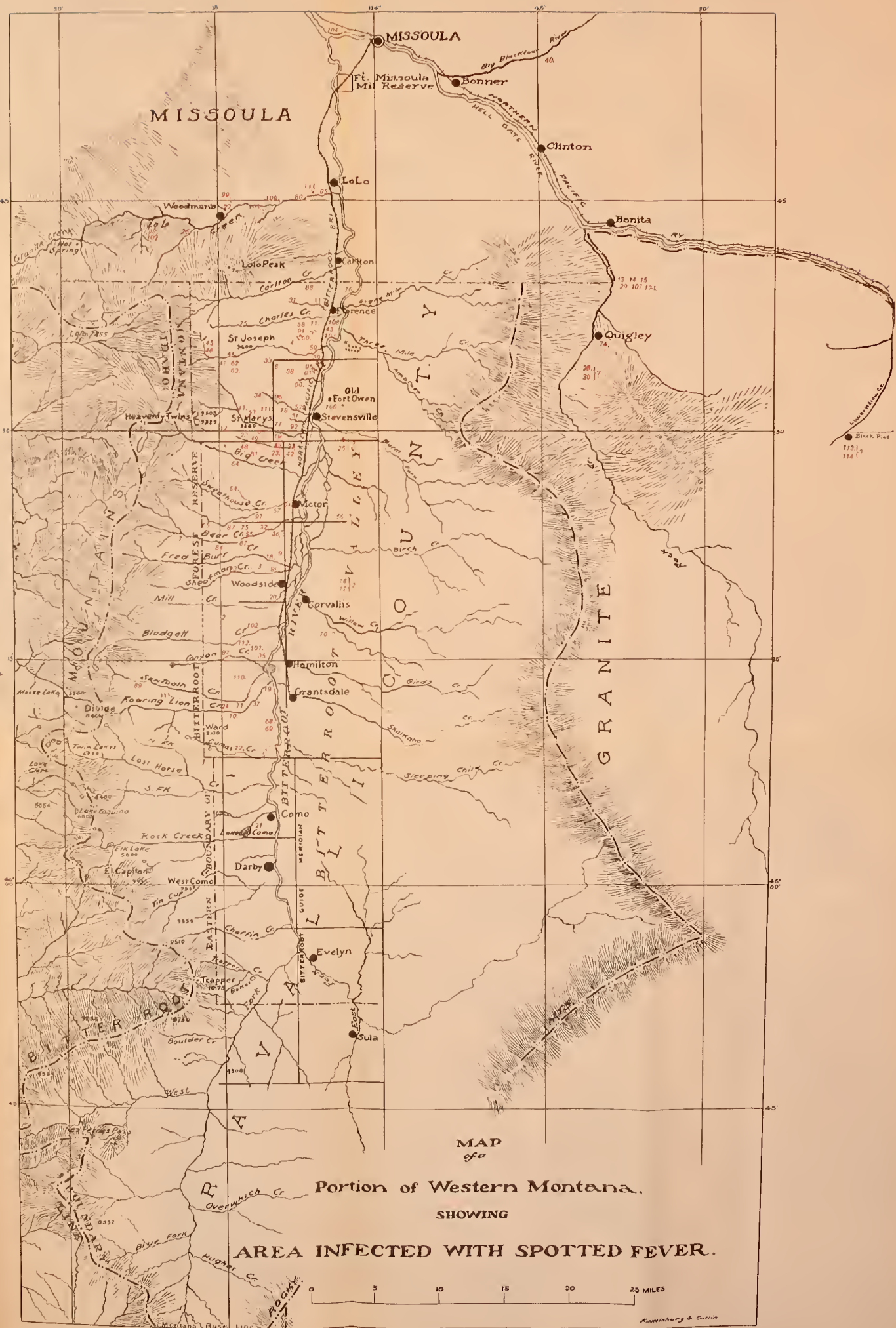
All occupations that cause the person to be exposed to the bite of ticks, such as stockmen, and especially sheep herders, miners, prospectors, lumbermen, ranchmen, and those whose duties take them into the brush, are subject to the disease.











MAP  
of a  
Portion of Western Montana,  
SHOWING  
AREA INFECTED WITH SPOTTED FEVER.

0 5 10 15 20 25 MILES

Amesbury & Corbin



## 5. AGE.

Persons from 15 to 50 years of age more often contract the disease, as during that period they are more actively engaged in outdoor work. The youngest case was 18 months and the eldest 74 years old.

## 6. SEX.

In 121 cases, 76 were males and 45 females, the difference being probably due to the greater liability to exposure of men on account of occupation.

## 7. THE PARASITE.

In the spring of 1902 Dr. A. F. Longeway, secretary of the Montana State Board of Health, engaged the services of Drs. L. B. Wilson and W. M. Chowning, of the University of Minnesota, to investigate the "spotted (tick) fever" then prevailing in the Bitter Root Valley. These gentlemen published the results of their work in the Journal of the American Medical Association July 19, 1902, and in the report of the Montana State Board of Health for 1901-2.

Surgeon-General Wyman, of the Marine-Hospital Service, detailed Surg. J. O. Cobb to also investigate the disease, and his report was published in the Public Health Reports, volume 17, No. 33, August 15, 1902.

The same year Dr. F. F. Westbrook, of the University of Minnesota, visited Missoula and confirmed the findings of Drs. Wilson and Chowning. His report will be found in the biennial report of the Minnesota State Board of Health for 1901-2.

Wilson and Chowning noticed ovoid intracorpuseular bodies in stained preparations of the blood from their earlier cases. They did not determine the character or significance of these bodies until they examined the fresh blood of case No. 94, when they found ovoid intracorpuseular bodies showing amoeboid movements. These observations they confirmed in all the later cases which they examined. To Wilson and Chowning, then, belongs the credit of discovering a parasite which is very *probably* the cause of spotted (tick) fever.

Parasites in the red-blood cells are rather common in the animal kingdom. The two which I desire to mention especially are those of malaria and of Texas cattle fever. The parasite found in the red-blood corpuscles of persons suffering from spotted fever apparently lies between these two. Unlike most malarial parasites, it is not pigmented, but, like them, it shows amoeboid movements, thus differing from the *Pyrosoma bigeminum*, which is nonpigmented and without motion. Again, one form of the parasite found in spotted fever is arranged in pairs in the red-blood cells, closely resembling the double form of *Pyrosoma bigeminum*.

In my studies upon the cause of spotted (tick) fever I had the opportunity of examining the blood, both fresh and stained, in a number of cases. Two cases were in hospital in Missoula, and daily examinations were made. In the fresh blood a few cells were found to contain parasites. Three forms were seen. The most common was a single ovoid body, refractile, situated within the cell, usually near its edge. When the slide is warmed this body possesses the power of projecting quite rapidly pseudopodia and a slight change of position. This form, which is apparently an early or young form, is about 1.5 to 2 micra in length, and 0.5 to 1 micron in width at its widest part. It closely resembles the earliest intracorpuscular parasites of æstivo-autumnal malaria. (See Pl. II, figs. 4, 5.)

Another form, not so common, was larger, being about 2 to 2.5 by 1 to 1.5 micra, larger at one end and showing in the larger end a dark granular spot; this was also amoeboid. (See Pl. II, fig. 6.)

The third form noted was arranged in pairs, distinctly pyriform, with the smaller end approaching, and in two cases a fine thread uniting the small ends was seen. Motion was not observed in this form, but the spot mentioned in the second form was seen. (See Pl. II, fig. 9.)

Great difficulty was experienced in staining the organism. A number of stains were used, but the most satisfactory results were obtained by the use of Wright's stain, followed by Loeffler's blue. Carbolized Unna's polychrome methylene blue also gave fair results, heat fixation at 120° C. for twenty minutes being used. I was unable to find the paired forms in stained preparations, though Drs. Wilson and Chowning informed me that they had no difficulty in doing so. By a reference to Pl. I, figs. 1 and 2, it will be seen that the parasite takes the stain more deeply at one end and is only faintly outlined in its periphery. Sometimes it has only a central stained spot surrounded by a clear unstained space. (See Pl. I, fig. 3.)

The parasites are never found in very large numbers, it being usually necessary to search several fields of the slide to find one. Sometimes they occur in groups, two or three infected cells being found in one field. In both fresh and stained preparations extracorpuscular bodies closely resembling the small single intracorpuscular form were seen. I was unable to definitely decide the character of these bodies, but am strongly inclined to think that they are the young form of the parasite which has not yet invaded the red cells.

I had the opportunity to examine the fresh and stained blood from cases in the Bitter Root Valley of smallpox, typhoid fever, measles, scarlet fever, rheumatic fever, pneumonia, pernicious anæmia, some surgical cases, and from healthy persons, but did not note in any of them any bodies, either intra or extra corpuscular, resembling in any



way the bodies above described as being found in the fresh and stained blood of persons suffering from spotted (tick) fever.

In the cases of spotted (tick) fever which I had the opportunity of examining I had no great difficulty in finding both in fresh and stained preparations the bodies above described. Their constancy in the blood of persons suffering with spotted fever, their persistence for some time in the blood of these persons after recovery, their absence from the blood of persons suffering from other diseases and of healthy persons makes it very probable that they are the cause of the disease, and that one more has been added to the rapidly growing list of diseases of man due to animal parasites.

Cultures were made by Wilson and Chowning and by myself from the blood of patients during life and from the organs and tissues at autopsy, and the only bacterial growth obtained was *Staphylococcus epidermidis albus*, *Staphylococcus pyogenes aureus* and *albus*, *Bacillus coli*, and in one case an anærobic spore-bearing organism was obtained from the spleen. No one organism was constant, and from some cases no growth at all was obtained.

In the table which follows is gathered a complete collection of all the cases which have been reported by the physicians of western Montana since 1885, when the disease first attracted attention. Cases 1 to 114 were compiled by Wilson and Chowning and the remaining cases by myself.

Table showing cases of spotted (tick) fever

Case No.	Physician's name and address.	Year.	Date of onset of symptoms.	Patient's initials.	Sex.	Age.	Occupation.
1	J. F. Coughenour, Corvallis.	1885	June 25	J. M .....	Male ...	36	Prospector.....
2	.....do.....	1886	May 3	H. T .....	.....do...	30	Lumberman.....
3	.....do.....	1888	May 7	Mrs. W.....	Female..	37	Housekeeper .....
4	R. Gwinn, Missoula.....	1888	Spring..	F .....	Male ...	35	.....do.....
5	.....do.....	1888	.....do.....	.....do.....	.....do...	25	Laborer .....
6	.....do.....	1889	.....do.....	Half-breed .....	.....do...	20	.....do.....
7	.....do.....	1889	.....do.....	.....do.....	Female..	6	.....do.....
8	.....do.....	1889	.....do.....	.....do.....	Male ...	12	.....do.....
9	J. F. Coughenour, Corvallis.	1890	June 22	W. J .....	.....do...	30	Laborer .....
10	.....do.....	1891	June 17	D. S.....	.....do...	40	Farmer .....
11	E. A. Crain, Missoula .....	1891	.....do.....	L. D .....	Female..	a 17	Farmer's daughter.
12	W. B. Parsons, Missoula....	1891	May ...	Z. H .....	Male ...	35	Hotel.....
13	.....do.....	1891	May 20	F. C.....	.....do...	48	Trapper .....
14	.....do.....	1891	May 26	C. M .....	.....do...	51	.....do.....
15	.....do.....	1891	July 20	L. P .....	.....do...	10	.....do.....
16	J. F. Coughenour, Corvallis.	1892	Apr. 27	Mrs. J. C.....	Female..	26	Housekeeper .....
17	.....do.....	1892	June 2	Mrs. C.'s babe.	Male ...	2d	.....do.....
18	E. A. Crain, Missoula .....	.....do.....	.....do.....	Name forgotten.	.....do...	a 30	Laborer .....
19	.....do.....	.....do.....	.....do.....	Mrs. M. G .....	Female..	a 28	Housewife.....
20	Geo. McGrath, Hamilton ...	1893	June .....	.....do.....	Male ...	a 11	.....do.....
21	.....do.....	1893	May .....	.....do.....	.....do...	a 40	Laborer .....
22	J. T. Brice, Stevensville ..	1895	.....do.....	O. O .....	.....do...	45	Farmer.....
23	.....do.....	1895	.....do.....	Mrs. A. A.....	Female..	40	Housewife.....
24	Geo. McGrath, Hamilton .....	1895	.....do.....	.....do.....	Male ...	a 8	.....do.....
25	J. T. Brice, Stevensville ..	1896	.....do.....	J. S .....	.....do...	44	.....do.....
26	J. J. Buckley, Missoula .....	1896	June .....	.....do.....	.....do...	26	Lumberman.....
27	G. T. McCullough, Missoula	1896	May 1	Ed. W .....	.....do...	26	Ranchman .....
28	W. B. Parsons, Missoula .....	1896	May .....	G. B .....	.....do...	32	.....do.....
29	.....do.....	1896	.....do.....	F. L .....	Female..	18	.....do.....
30	.....do.....	1896	.....do.....	— P .....	Male ...	.....do...	.....do.....
31	J. T. Brice, Stevensville ..	1897	.....do.....	J. F. W .....	.....do...	60	Farmer .....
32	.....do.....	1897	.....do.....	J. N .....	.....do...	a 60	.....do.....
33	.....do.....	1897	Apr .....	R. C .....	.....do...	21	.....do.....
34	.....do.....	1897	June .....	Mrs. C. M.....	Female..	40	Housewife.....
35	J. J. Buckley, Missoula .....	1897	Spring .....	.....do.....	Male ...	30	Lumberman.....
36	.....do.....	1897	.....do.....	J. H .....	.....do...	27	Farmer.....
37	J. W. Howard, Hamilton ..	1898	June 27	A. D .....	.....do...	43	.....do.....
38	J. T. Brice, Stevensville....	1899	May 19	D. M.....	.....do...	14	Schoolboy.....
39	.....do.....	1899	June .....	W. H .....	.....do...	30	Farmer.....
40	C. A. Crain, Missoula .....	1899	.....do.....	H. M .....	Female..	12	.....do.....



reported by physicians of western Montana.

About what day of illness did spots appear.	Death on what day of disease, or convalescence beginning about what day.	Remarks.
Fifth .....	Died eleventh day .....	Made 3 visits—July 2, 3, 4, 1885. Spots present at my first visit. Diagnosed case "typhoid fever."
Fourth .....	do .....	
Sixth .....	Beginning of lysis on fifteenth day.	
Third .....	Died sixth day .....	
Third or fourth .....	Convalesced eighteenth day.	
Third .....	Died fifth day .....	
do .....	Died seventh day .....	
do .....	do .....	
Fifth .....	Died eleventh day .....	
Fourth .....	Died tenth day .....	
No record .....	Recovered .....	This case occurred in a year when there were many deaths from spotted fever from Carlton to Corvallis. It was then called by the valley physicians "black measles."
Third .....	Died sixth day .....	This man lived in Stevensville. A short time before he was taken sick he was on the west side of the river and slept out in the mountains.
do .....	Died seventh day .....	
do .....	Died sixth day .....	
do .....	2 or 3 weeks .....	
do .....	Died eighth day .....	Mrs. C. had been delivered of male babe 4 days before her death. Early in the second morning after birth the babe's grandmother called my attention to the child's fever and jaundiced appearance.
Had but little eruption.	Began to get better on ninth or tenth day.	Had but few spots; began to get better on ninth or tenth day of his sickness.
No record .....	Recovered .....	I can give no good account of them. The man, as near as I can remember, was under my care for about 3 weeks, then went to his relations at Wausau, Wis. The case of the female was slight.
do .....	do .....	
Third .....	Died about thirteenth day.	
do .....	Died twelfth day .....	
do .....	Died eighth day .....	
do .....	Died twelfth day .....	
Don't remember .....	Died about eleventh day.	Considerable swelling of legs and face last day or two.
Fourth .....	Died tenth day .....	
Can not say .....	Died about eighth day .....	Impossible to find any records in this case in St. Patrick's Hospital records.
Fourth .....	Died eighth day .....	
About third day .....	Died in a few days .....	
do .....	do .....	
do .....	do .....	
Third .....	Died ninth day .....	
do .....	Died eighth day .....	
do .....	Died tenth day .....	
do .....	Died eighth day .....	
do .....	do .....	Case came from Hamilton and taken to St. Patrick's Hospital; only lived 2 days. Was broken out thoroughly on arrival; could get no history from him. A post-mortem held; only thing apparently abnormal was spleen largely increased in size.
Fourth .....	Recovery .....	This man was seen by me in consultation with the late Dr. G. F. Mills, who had charge of the case. It presented the usual type. He had marked delirium, was abundantly "spotted," but made a good recovery.
About fourth .....	Recovered at the end of the fourth week after attack. Dismissed at end of five and a half weeks from date of attack.	Was called to see this case on July 9, he having been attended by others prior to this. Found him entirely comatose and learned that had existed for 3 days prior. Respirations hurried. Temperature but slightly above normal and the petechic abundant, many of which, by their coalescence, made a spot as large as 1 inch in width and 2 or 3 in length, all of which, later on, formed dry gangrene and sloughed to a depth including deep fascia.
Third .....	Recovered.	
Fourth .....	Died tenth day.	
No record .....	Recovered after about 3 weeks treatment.	Child from "Big Blackfoot" country, after disease was well developed. The spots were not as general as in the cases I had before, and were only general in distribution over the region of shoulders and spine.

Table showing cases of spotted (tick) fever reported

Case No.	Physician's name and address.	Year.	Date of onset of symptoms.	Patient's initials.	Sex.	Age.	Occupation.
41	R. Gwinn, Missoula.....	1899	June....	M.....	Male...	30	Farmer.....
42	do.....	1899	do.....	W., Mrs.....	Female..	39	Housewife..
43	do.....	1899	do.....	B.....	Male...	18	Farmer.....
44	do.....	1899	do.....	F.....	do.....	45	do.....
45	do.....	1899	do.....	T. (2 children)	Male and	3, 5	.....
46					female.		
47	do.....	1899	do.....	J. T.....	Male...	50	Prospector..
48	do.....	1899	do.....	Mrs. J. A.....	Female..	40	Housewife..
49	do.....	1899	do.....	Mrs. S.....	do.....	45	do.....
50	do.....	1899	do.....	M. V.....	do.....	9	.....
51	do.....	1899	do.....	.....	Male...	30	Lumberman..
52	do.....	1899	do.....	.....	do.....	30	do.....
53	do.....	1899	do.....	.....	do.....	33	do.....
54	T. H. Hanbridge, Victor...	1899	Apr. 24	L. W.....	Female..	12	Schoolgirl..
55	do.....	1899	May 4	Mrs. B. W.....	do.....	18	Housekeeper..
56	J. W. Howard, Hamilton ..	1899	July....	— J.....	Male...	2½	.....
57	do.....	1899	do.....	H. M.....	do.....	2½	.....
58	do.....	1899	June 25	.....	do.....	35	sawmill man.....
59	J. T. Brice, Stevensville....	1899	May....	B. R.....	Female..	3	None.....
60	do.....	1899	Apr.....	Mrs. J. W.....	do.....	22	Housekeeper..
61	R. Gwinn, Missoula.....	1900	June....	F. T.....	Male...	70	Farmer.....
62	do.....	1900	do.....	Mrs. L.....	Female..	35	Housekeeper..
63	do.....	1900	.....	.....	Male...	30	Laborer.....
64	T. H. Hanbridge, Victor...	1900	Apr. 30	Mrs. A.....	Female..	42	Housekeeper..
65	do.....	1900	May 13	K.....	Male...	4	.....
66	do.....	1900	May 18	Baby.....	Female..	1½	.....
67	do.....	1900	Apr. 15	R. B.....	Male...	40	Stone mason ..
68	Geo. McGrath, Hamilton ..	1900	May 2	T.....	do.....	a 9	.....
69	do.....	1900	May 8	B.....	do.....	a 2½	.....
70	do.....	1900	May 6	H.....	Female..	a 10	.....
71	do.....	1900	Apr.....	Mrs. W.....	do.....	a 40	Housewife..
72	do.....	1900	Apr. 16	Mrs. M.....	do.....	a 55	.....
73	do.....	1900	June....	— N.....	Male...	a 17	.....
74	Geo. Putney, Missoula.....	1900	Mar. 30	F. L.....	Female..	a 20	None.....
75	H. F. Brethnour, Hamilton.	1901	May 6	S.....	Male...	25	Lumber jack ..
76	J. T. Brice, Stevensville....	1901	May —	B.....	Female..	3	None.....
77	do.....	1901	May —	J. P.....	Male...	25	Laborer.....
78	do.....	1901	May 24	— R.....	do.....	12	Schoolboy.....

## by physicians of western Montana—Continued.

About what day of illness did spots appear.	Death on what day of disease, or convalescence beginning about what day.	Remarks.
Third.....	Died tenth day.....	Complicated with pneumonia.
do.....	Died eighth day.....	
Second.....	Died fourth day.....	
Third.....	Died seventh day.....	
do.....	do.....	
Second.....	Died third day.....	Very violent attack after exposure.
Third.....	Convalescent twenty-first.	
do.....	do.....	
Fourth.....	Convalescent forty-second.	Mild and prolonged attack.
Third.....	Died sixth day.....	
do.....	do.....	
Third.....	Died fifth day.....	Relapsed after abortive treatment.
Second.....	Died sixth day.....	
Fourth.....	Convalescence set in on twelfth day. Fever dropped entirely out twenty-second day.	
Fourth or fifth.....	Recovered. Convalescence began ten days after coming under my observation and was dismissed at the end of three and a half weeks.	Temperature about 103; pulse exceedingly rapid; respiration between 40 and 50; petechia well defined and abundant; extreme prostration and marked jactitation. The foregoing symptoms continued until beginning convalescence.
Do not know.....	Recovered. Convalescence began at about the end of third week after attack, but not dismissed for about four and a half weeks from the date of attack.	Symptoms same as case No. 56, but in a more advanced stage, with a correspondingly increased state of petechia.
Third or fourth.....	Died. Saw patient first at about 9 p. m., and he died at about 8 the next a. m.	
Third.....	Died ninth day.....	Sent to Sister's Hospital, Missoula. Sick about 24 days. 2 months before recovery was complete. Treated by Dr. W. P. Mills at hospital. Had a low fever record; eruption well marked.
do.....	Recovered.....	
Seventh.....	Died about seventh day.	Complicated by gangrene.
Third.....	Died about fourteenth day.	
do.....	Died about seventh day.	
do.....	Died eleventh day.....	
Second.....	Died sixth day.....	No. 66 is a niece of No. 82 and died the year before.
Third.....	Died eighth day.....	
Fourth.....	Died seventh day.....	Recovered.
Third.....	Last visit May 25, 1899.....	
Can not tell at first visit.	Last visit May 20.....	Do.
About fifth day.....	Last visit May 23, 1902.....	Do.
Third, so says husband.	Died on third day of eruption.	First and last visit the morning of day she died.
Fourth, so says her son.	Died on tenth day of disease.	Considerable swelling of legs and face the last 2 or 3 days.
Do not know.....	Died about thirteenth day.	
About one week after first symptoms appeared, but the symptoms came on gradually and I did not see her during first 6 or 7 days, so I can not say definitely.	Died on eleventh day..	In this case the symptoms were about 3 days in reaching their height. She became slightly more ill with malarial fever, etc., each day, very much as a very malignant case of typhoid would do. Delirium about fourth day. Hypostatic pneumonia beginning at this time. I saw her first at the end of the first week, when she had been delirious for 3 days. She is supposed to have contracted the disease at Quigley, where she was visiting just previous to her illness.
Sixth.....	Convalescent sixteenth day.	Complicated with pneumonia; patient especially rugged.
Third.....	Died tenth day.....	
do.....	Died ninth day.....	
do.....	Recovered.....	Sick 23 days when convalescence began. Disease taken regular course from onset. First symptom same as other cases of same disease.

Table showing cases of spotted (tick) fever reported

Case No.	Physician's name and address.	Year.	Date of onset of symptoms.	Patient's initials.	Sex.	Age.	Occupation.
79	J. T. Brice, Stevensville .....	1901	May —	R. ....	Female.	13	Schoolgirl .....
80	J. J. Buckley, Missoula .....	1901	May 17	A. H. ....	do .....	18	Attending school.
81	T. H. Hanbridge, Victor .....	1901	Apr. 20	R. C. ....	Male ...	62	Laborer .....
82	do .....	1901	Apr. 2	G. B. ....	do .....	35	do .....
83	do .....	1901	May 4	Mrs. R. ....	Female.	62	Housekeeper .....
84	do .....	1901	July 12	M. B. ....	do .....	7	do .....
85	G. T. McCullough, Missoula.	1901	Mar. 27	B. R. ....	do .....	3	do .....
86	do .....	1901	Mar. 20	J. F. ....	Male ...	31	Lumberman .....
87	Geo. McGrath, Hamilton .....	1901	July 1	Mrs. M. H. ....	Female.	a 37	Nurse .....
88	W. B. Parsons, Missoula .....	1901	June —	J. H. ....	Male ...	35	Lumber jack .....
89	N. F. Brethnour, Hamilton.	1902	May 13	Mrs. J. D. ....	Female.	33	Housewife .....
90	J. T. Brice, Stevensville .....	1902	Apr. 20	Mrs. E. B. ....	do .....	a 40	Housekeeper .....
91	do .....	1902	May 15	A. G. ....	Male ...	22	Farmer .....
92	do .....	1902	Apr. 27	Mr. E. ....	do .....	74	do .....
93	do .....	1902	May 24	J. A. P. ....	do .....	a 23	Laborer .....
94	do .....	1902	May 25	A. R. ....	Female.	a 6	None .....
95	do .....	1902	June 3	J. O., jr. ....	Male ...	2	do .....
96	do .....	1902	June 17	D. McD. ....	do .....	34	Lumberman .....
97	J. C. Burton (D. O.), Missoula	1902	May 23	Mrs. V. R. W. ....	Female.	65	Wife of farmer ...
98	R. Gwinn, Missoula .....	1902	June 1	B. J. H. ....	Male ...	38	Timber inspector.
99	do .....	1902	Apr. 22	McN. ....	Female.	30	Housekeeper .....
100	do .....	1902	Apr. 8	B. J. ....	Male ...	45	Common laborer .
101	Geo. McGrath, Hamilton .....	1902	Mar. 17	A. M. ....	Female.	12	Schoolgirl .....
102	do .....	1902	Apr. 13	W. E. ....	Male ...	9	Schoolboy .....
103	do .....	1902	Apr. 16	A. F. ....	do .....	35	Laborer .....
104	G. T. McCullough, Missoula.	1902	Apr. 20	C. D. ....	do .....	20	Teamster .....
105	do .....	1902	Apr. 10	P. W. ....	do .....	9	do .....
106	Dr. W. B. Parsons, Missoula.	1902	Apr. 12	McG. ....	Female.	4	None .....
107	do .....	1902	May 10	H. M. ....	Male ...	9	do .....
108	do .....	1902	May 25	G. R. ....	do .....	52	Farmer .....
109	E. W. Spottswood, Missoula.	1902	May 6	J. W. ....	do .....	40	Lumber cruiser ...
110	Dr. Owen, Hamilton .....	1892	Apr. 16	Mrs. S. ....	Female.	55	Housewife .....
111	do .....	1898	May 25	R. McF. ....	Male ...	30	do .....
112	do .....	1898	June 10	Mrs. J. H. ....	Female.	24	Housewife .....
113	T. G. Heine, Butte .....	1893	(b)	W. H. ....	Male ...	a 34	Miner .....
114	do .....	1893	(c)	Mrs. W. H. ....	Female.	a 30	Housewife .....
115	Dr. McGrath, Hamilton .....	1903	Apr. 7	O. G. ....	do .....	8	Child .....
116	Dr. McCullough, Missoula	1903	Apr. 19	Mrs. F. D. ....	do .....	18	Housewife .....

a About.

b Early in March.

c Ten days later than husband.



## by physicians of western Montana—Continued.

About what day of illness did spots appear.	Death on what day of disease, or convalescence beginning about what day.	Remarks.
Third.....	Died eighth day.....	This patient made a good recovery though a very severe case and remarkably well spotted. This patient drank no water during the season.
Fifth.....	Recovered.....	
Third.....	Died fifth day.....	This is a daughter of No. 82, but was not living on the same ranch.
Fourth.....	Died seventh day.....	
do.....	Died eleventh day.....	
do.....	Died eighth day.....	Very typical case. Patient conscious until hour or two before death. Full report obtained before.
About fourth.....	Died seventh day.....	
About fifth.....	Died tenth day.....	Saw patient first in my office on second day of illness complained of. Pains in head, back upper and lower limbs, soreness of muscles in all parts of body. Temperature, 102; pulse, 90; respiration, 24. Temperature did not raise above 103; was normal 24 hours before death.
Third.....	Recovered twenty-first day.	
do.....	Died sixth day.....	Saw him first about 3 hours before death. Had been alone most all the time; could get no history. Spots well defined.
do.....	Died eleventh day.....	
do.....	Died ninth day.....	Saw him first 33 hours after onset of disease. History same as above. Temperature, 103; pulse, 90; respiration, 24. Taken regular course of disease. Died on thirteenth day.
Fourth.....	Died eighth day.....	
Unknown.....	Died about ninth day.....	Began with chills and vomiting, with a rapid rise of temperature. Bowels were loose from onset of disease; urine scanty and highly colored. At first visit, two days after onset of disease, found temperature 105; pulse rate 104, and respiration 32. The temperature was kept under 103 by the use of baths, the pulse rate did not vary materially, and the respirations gradually increased to 45 per minute. Ten hours before death occurred temperature fell to 95 and the spots all became darker.
Third.....	Died seventh day.....	
Second.....	Died eleventh day.....	Abortive treatment; blood showed protozoan.
Third.....	Died eighteenth day.....	
do.....	Died thirteenth day.....	Abortive treatment used by patient at first attack. Abortive treatment; threatened gangrene of right toes. Circulation quite rapid at end of two months. Delirious much of the time after Apr. 17 until death.
About fifth day.....	Died sixth day.....	
A few third day.....	Convalescent eighth day.	Convalescence beginning about twelfth day of disease.
Ninth.....	Convalescent tenth day.	
do.....	Convalescent ninth day.	No. 108 is the only one which recovered. He had been bitten by two ticks a few days before taken sick.
About fourth.....	Recovery twenty-first day.	
do.....	Died Apr. 23, tenth day.	Convalescence very slow in each case; it was about 10 or 12 weeks before they could work, and their health was never so good afterwards while I knew them.
Fourth.....	Died about twelfth day.	
About fifth.....	Recovered.....	Systematic treatment with quinine; parasites in blood. Blood showed parasites.
About third.....	Died ninth day.....	
Third.....	Died sixth day.....	Convalescence began about eighteenth day; last medicine given 5 weeks after onset of disease.
do.....	do.....	
do.....	Recovered in three weeks.	Convalescent about fourth week.
do.....	Died ninth day.....	
Fourth.....	Convalescence began about eighteenth day; last medicine given 5 weeks after onset of disease.	Little earlier than husband.
Death on eighth day.....	Death on ninth day.....	
This I am not certain, but I think about 8 or 10 days.	Convalescent about fourth week.	About 8 or 10 days.
About 8 or 10 days.....	Little earlier than husband.	
Third.....	About fifteenth day.....	Eighth day.....
do.....	Eighth day.....	

Table showing cases of spotted (tick) fever reported

Case No.	Physician's name and address.	Year.	Date of onset of symptoms.	Patient's initials.	Sex.	Age.	Occupation.
117	Dr. Brooke, Stevensville...	1903	Apr. 20.	J. H. D.....	Male....	34	Farmer.....
118	Dr. Bryce, Stevensville....	1903	....do....	C. F.....	....do....	48	Lumberman.....
119	.....do.....	1903	Apr. 25	R. S.....	Female..	5	Child.....
120	Dr. Mills, Missoula.....	1903	Apr. 28	C. W.....	Male....	28	Ranch hand.....
121	Drs. Parson and Brown, Missoula.	1903	May 11	Mrs. L. M.....	Female..	30	Housewife.....



by physicians of western Montana—Continued.

About what day of illness did spots appear.	Death on what day of disease, or convalescence beginning about what day.	Remarks.
Fourth .....	Eighth day .....	Blood showed Parasites.
Third .....	Convalescence began about eighteenth day.	Blood showed parasites. Systematic treatment with quinine.
.....do .....	Convalescence began twelfth day.	Blood examination not permitted. Quinine treatment.
Seventh .....	Died fourteenth day....	Blood showed parasites. No quinine.
Third.....	Convalescent fifteenth day.	Blood showed parasites. Quinine treatment.

## 8.—METHOD OF INFECTION.

The life history of the organisms of malaria and Texas fever naturally suggested that some insect was concerned in the transmission of the disease. On investigation it was found that the ticks appeared in the valley about the last of February, but were inactive until the middle of March or first of April, the first cases of fever appearing about the last of March. The ticks begin to diminish greatly in number from about June 1, and after the middle of July very few are seen; the cases of fever also begin to diminish about June 1, the latest date on which the disease has been known to occur being July 20.

Mosquitoes do not appear in the valley until after the first cases of fever develop, and remain some time after the last cases appear. Bedbugs and other house insects, I think, were well excluded, by the fact that there has never been known an instance in which two cases occurred the same year in the same house.

On a closer study of the cases of spotted (tick) fever it was always found that there was a history of tick bites about one week before the onset. In four cases there was a history of a single bite two, three, five, and seven days, respectively, before the initial symptoms. The usual time between the bite and the onset of the fever is about seven days. If the tick transmits the disease, it may be asked, Why do not more persons become infected, and why is the infection confined to the west bank of the Bitter Root River? I think this may be answered by the very obvious fact that the tick is unable to travel any great distance, unless carried on some person or object. Again, it is very unusual for a tick to bite a person and not be discovered in a short while, and the result is the death of the tick. If, as in Texas fever, the development of the parasite takes place in the female tick and the young ticks transmit the infection, the very small number of ticks which escape detection on persons explains the small number of infected ticks. Where do the female ticks get their infection? I examined a recovered case twenty-four days after discharge by the physician and had no trouble in finding the parasite in the fresh blood. This child had been out of doors for over two weeks, and if a female tick (ticks were quite numerous near the house) had bitten her and escaped destruction the parasites in the blood taken in by the tick would have undergone development and the young ticks, when hatched out, would be ready to infect prospective victims.

While the above facts and conclusions tend strongly to the belief that the ticks are necessary for the transmission of the disease, the actual fact can not be proved scientifically until carefully controlled experiments are made on nonimmune persons.

## TICKS.

As many ticks as it was possible to obtain were collected in the Bitter Root Valley; twenty-four, representing what were thought to be different species, were sent to the Hygienic Laboratory of the Service in Washington, D. C., for classification. They were referred by the Director to Dr. Ch. Wardell Stiles, Zoologist of the Laboratory, for determination, and he reports that—

All of these specimens belong to the genus *Dermacentor*. There is considerable variation among them, but so far as I have been able to make out, this variation does not extend beyond the limits usually found in one and the same species in this group. Most of the material is not in the best condition for determination, but so far as I am able to discover, I can recognize as yet no specific difference between these specimens and *Dermacentor reticulatus*. I would therefore make the provisional diagnosis of *Dermacentor reticulatus*.

The ticks in box No. 1 have laid numerous eggs, and I have developed the six-legged stage from them. I have now made arrangements to place these young ticks on cattle and develop all of the various stages. With fresh material of this kind I shall be able to determine whether the variations noticed extend beyond the limits of specific value, and also whether there is any reason for me to change my opinion that these represent the species known to zoologists as *Dermacentor reticulatus*.

## SYMPTOMS.

## INCUBATION.

This is from three to ten days, usually about seven. For a few days the patient may have chilly sensations, malaise, and nausea; finally there is a distinct chill, and the person takes to bed. There is some pain in the back and head; soreness of the muscles and bones, causing a sensation as if the limbs were in a vise; bowels constipated; tongue with heavy white coat, red edge and tip; conjunctivæ congested, becoming yellowish; urine usually small in amount, with albumin and a few casts; slight bronchitis after a few days; nose bleed, sometimes quite severe, is always present.

## FEVER.

Before the distinct chill there is little or no fever in the morning, with a slight rise in the afternoon. After the chill there is an abrupt rise, and from then on the fever gradually rises in the evening, with a slight morning remission. The maximum is usually reached on the eighth to the twelfth day; then, in a favorable case, gradually falls, becoming normal about the fourteenth to the eighteenth day, usually going to subnormal for a few days. In fatal cases the fever remains high, from  $104^{\circ}$  to  $105^{\circ}$  or  $106^{\circ}$ , and the morning remissions are very slight or not present.

## CIRCULATORY SYSTEM.

The pulse appears out of all proportion to the temperature, usually running from 110 to 140, a pulse of 120 being not unusual with a temperature of 102°. It is rather thready, though sometimes full and strong, occasionally dicrotic in the first week. Red blood counts show a progressive decrease in red cells, but as soon as the temperature becomes normal an increase begins. The white blood corpuscles are increased in number, varying from 8,000 to 12,000. A differential count in two cases gave an average of—

	Per cent.
Polymorphonuclear leucocytes .....	77.7
Large mononuclear leucocytes .....	11.4
Small lymphocytes.....	10.0
Eosinophiles.....	.9
Total.....	100.0

This shows as its most interesting feature an increase in the large mononuclears.

There was a steady, but never very rapid, decrease in the percentage of hemoglobin, one case going as low as 50 per cent.

The blood failed at all times to agglutinate *bacillus typhosus*.

Fresh and stained blood showed the three forms of parasites described under etiology.<sup>a</sup>

## THE ERUPTION.

The eruption appears usually on the third day, first on the wrists and ankles, then on arms, legs, forehead, back, chest, and, last and least, on the abdomen. It is never very abundant on the abdomen, but the other portions of the body in some cases are literally covered by the eruption.

At first the spots are of a bright-red color, macular at all times, from a pin point to a split pea in size. At first they disappear readily on pressure and return quickly, but if the case is a severe one they soon become darker and in some cases are almost purple. From about the sixth to the tenth day of the disease they fail to disappear on pressure and are distinctly petechial in character. In favorable cases, about the fourteenth day they begin to lose their petechial character and disappear slowly on pressure. In some cases the eruption consists of small, brownish spots, giving a turkey-egg appearance, well shown by the photographs on pages 22 and 23.

As the fever declines the eruption begins to fade; but a slight return of fever or a free perspiration will cause it to show distinctly. I am informed that, following a warm bath in a case ten months recov-

<sup>a</sup>The average normal red blood count at this elevation (3,500 feet) gives over 5,500,000.



ERUPTION TICK FEVER; TWO HOURS AFTER DEATH.









ERUPTION TICK FEVER; TWO HOURS AFTER DEATH.

ered, the spots showed distinctly. I have seen them in a case twenty-four days after discharge.

When convalescence is well advanced desquamation begins and extends over the entire body. In very severe cases there may be gangrene of the fingers or toes, and still more frequently of the skin of the scrotum and penis. The skin is always jaundiced to a greater or less degree. This is usually first noticed in the conjunctivæ, the vessels of which are congested from the outset.

#### DIGESTIVE SYSTEM.

The tongue at first has a heavy whitish coat, with red edge and tip; later the coat becomes dark brown and the teeth are covered with sordes. At first there may be a little nausea, but the appetite is often good throughout the first week. In fatal cases nausea becomes more persistent during the second week and lasts until the end. Constipation is present throughout the course of the attack. Tympanites is never excessive; gurgling in right iliac fossa occasionally. The liver is usually moderately enlarged. The spleen is enlarged early and may extend 1 or 2 inches below the costal margin.

#### URINARY SYSTEM.

The urine is decreased to about one-half its normal amount for the twenty-four hours; small amount of albumin in all cases examined; granular, hyaline, and epithelial casts.

#### RESPIRATORY SYSTEM.

The respiratory rate is always increased, usually varying from 26 to 40 per minute, in some cases reaching 50 to 60; regular, but often shallow. In the second week there is always a slight bronchitis. Lobar pneumonia is a frequent complication in fatal cases. Epistaxis is usually seen from the end of the first week.

#### NERVOUS SYSTEM.

Pain in head and back is usually severe during the first week. Soreness of the muscles and bones causes the patient to change position often in the endeavor to find a comfortable posture. The muscular soreness is often very severe, even in mild cases, and lasts until recovery. The mind is usually clear, even in severe cases, until within a few hours of the end. Pupils react normally to light and distance; no opisthotomus or other irritative symptoms.

## HISTORY OF CASES.

## CASE 115, 1903.

O. C., age 8 years, residence about 3 miles west and 1 mile south of Hamilton, about 1 mile east of case Mrs. J. D., case 89, 1902. (See map, p. 8.)

About April 1 two ticks were removed from right side of head, near middle line. The wounds became quite sore on the following day and the child complained of headache during the ensuing week. April 7 or 8 the child complained, in addition to headache, of soreness from site of bite down the side of head behind right ear and neck to shoulder. The post-cervical glands were enlarged, particularly on right side. At this time she complained of being chilly, though she did not have a marked rigor. She was feverish April 8, 9, and 10. On April 10 spots began to appear, first on the extremities.

She was first seen by Dr. G. B. McGrath, of Hamilton, on April 13.

Patient was seen by Drs. McGrath and Wilson April 24. Child seemed pale, weak, and easily tired, but otherwise well and able to play outdoors. Over the forearms, legs, thighs, and back there was a distinct mottling of the skin. Pressure over these areas increased the distinctness of the spots. Examination of fresh blood showed a few ovoidal bodies within red blood cells. Count showed—

Red blood corpuscles.....	4,720,000
Leucocytes .....	4,500
Hemoglobin (Tallquist).....	per cent.. 80

Post-cervical glands on right side still enlarged.

Patient examined again May 5 by Drs. Anderson, Hanbidge, and Wilson. Feeling much better, not as pale as on previous examination, and able to play longer without tiring. Pulse, 112; temperature normal.

Red blood corpuscles.....	4,824,000
Leucocytes .....	4,450
Hemoglobin (Tallquist).....	per cent.. 90

Fresh blood showed a few red blood corpuscles which contained the ovoidal bodies similar to those seen at first examination.

## CASE 116, 1903.

Mrs. F. D., age 18 years, married one and one-half years, mother of 7-months-old child. Residence on left bank of Lolo Creek, 1 mile west of Lolo store. (See map, p. 8.)

On April 12 or 13 Mrs. D. was with her husband with team in grove of small poplars 300 yards north of residence. On this day she was perhaps also across Lolo Creek, south of house; accurate information on this point could not be gained. Certainly the horse



ERUPTION TICK FEVER; TWELFTH DAY.







On April 19 the soreness became much worse, and shooting pains began radiating from the axilla through the shoulder, down the arm and side of the body. Patient had a severe chill, followed by high temperature and aching pains in back. These gradually extended to the whole body. Patient felt better on April 20 and 21 in the morning, but was worse again in the afternoon.

On April 22 she was brought to St. Patrick's Hospital, Missoula, and placed under the care of Dr. McCollough. On the evening of April 22 spots began to appear first on the wrist and ankles. On the morning of April 24 spots were well developed all over body, being of the small petechial type and quite rosy in appearance. Patient's mind at this time was quite clear (except for slight wandering immediately after awakening) and remained so until a few hours before death.

Patient examined April 24, 9 a. m., by Drs. McCollough, Gwinn, Spottswood, and Wilson. Fresh blood showed a few red cells which contained ovoidal bodies with amoeboid movements (an alcohol lamp was in front of concave mirror). Count showed—

Red blood corpuscles .....	4, 920, 000
Leucocytes.....	7, 400
Hemoglobin.....per cent..	100

Cultures with blood taken from the ear were made on agar and serum. These showed no growth after three days in the incubator.

Patient was examined again April 26 by Dr. Wilson. Condition was apparently the same as when last seen except the patient was more restless. Fresh blood showed many more infected cells than that collected April 24. Count showed—

Red blood corpuscles .....	4, 600, 000
Leucocytes.....	7, 600
Hemoglobin.....per cent..	80

Patient died at 10 a. m., April 27. (For temperature, pulse, etc., see accompanying chart.)

On the afternoon of April 24 Dr. Wilson, in company with Mr. D., examined the latter's ranch and searched for ticks in the locality where Mrs. D. was supposed to have gotten her infection. No ticks were found.

#### CASE 117, 1903.

J. H. D., age 34, residence one-half mile north and one-fourth mile west of Florence. (See map, p. 8.)

Was bitten on top of the head and on left arm by ticks on Thursday, April 16. Ticks, when removed on this date, were partially filled with blood, having evidently been in place for some time. Wounds were sore before removal of ticks and continued so until disease was well developed. On April 20 soreness of wound on head

extended over side of head and down neck with shooting pains to shoulder, arm, and hand. Patient had marked chill, followed by fever.

On April 20 spots appeared on hands and feet, extending up forearms and legs and appearing on back in a few hours. Patient was seen on this day by Dr. Brooke, of Stevensville. No record of pulse, etc., was kept, but the following figures were obtained from nurse after death of patient:

*Temperature.*

April 20.....	105.0	April 24.....	103.0
April 21.....	101.0	April 25.....	100.2
April 22.....	99.0	April 26.....	100.0
April 23.....	105.0	April 27.....	98.0

Pulse ran from 90 to 120 throughout the disease, until the last twenty-four hours. Respiration normal at first, became more rapid and labored until a few hours before death, then gradually grew weaker. Mind was clear throughout the course of the disease until a few hours before death. After initial constipation bowels were regular without medicine. Tongue was coated throughout course of disease.

Patient was examined April 27, at 2 p. m., by Drs. Brooke and Wilson. Temperature normal, pulse 108, respiration 30 and labored. Face and limbs much swollen. Mind fairly clear, but some stupor. Skin over whole of body, and especially of dependent portions, showed spots of dark red to purple in color and from 1 mm. to 3 cm. in diameter. Over the legs and forearms a marked marbled appearance was produced. Fresh blood showed relatively large numbers of red blood cells which contained parasites. Count showed—

Red blood corpuscles.....	4,368,000
Leucocytes.....	7,800
Hemoglobin.....per cent..	60

Patient died on April 28, 4 a. m. No autopsy was performed.

CASE 118, 1903.

E. F., age 48 years, residence 4 miles north of Stevensville, on main road. (See map, p. 8.) Had been bitten many times by ticks during the spring of 1903. Had no remembrance of any single severe bite shortly before illness. Was not feeling well on Sunday, April 19. Had a chill on April 20, followed by fever with morning remissions during the next two days. Spots began to appear April 22, first on extremities. Were well marked April 23, when patient was first seen by Dr. Bryce, of Stevensville. Patient at this time presented the usual symptoms of headache, fever (temperature 103), aching pains in back and limbs, and constipation. Patient was given calomel 10 grains and quinine sulphate 40 grains by the mouth. Patient examined

April 27,\* at 11 a. m., by Drs. Bryce and Wilson. Spots were numerous, large, and covering entire body, were rosy in appearance except on dependent portions, where they were somewhat darker in color. Temperature 101, pulse 104, respiration 26. Fresh blood showed a few red cells containing organisms. Count showed—

Red blood corpuscles .....	4,576,000
White blood corpuscles .....	7,300
Hemoglobin.....per cent..	70

At Dr. Wilson's suggestion, the patient's room was darkened, with apparent good results in allaying restlessness.

Patient examined again April 29 by Drs. Bryce, Johnson, and Wilson. Examinations of fresh blood showed many red blood cells containing organisms. Count showed—

Red blood corpuscles .....	3,820,000
Leucocytes.....	8,000
Hemoglobin.....per cent..	50

Patient examined again May 2 by Drs. Bryce, Anderson, and Wilson. Patient very weak; condition otherwise much as before. Spots somewhat darker on dependent portions, but more rosy over remainder of body. Temperature 102.5, pulse 120, respiration 28. Patient had had only strychnine for the last twenty-four hours. Given subcutaneous injection of quinine hydrochlorate 20 grains at time of visit. Examination of fresh blood showed a few organisms in red cells. Count gave—

Red blood corpuscles .....	3,920,000
Leucocytes.....	8,500
Hemoglobin.....per cent..	60

(Specimen taken from same point as that of April 27.)

Patient passed into a state of semiconsciousness, gradually increasing to total unconsciousness, which gradually passed away, having lasted seventy-two hours.

Pulse about 120, temperature ran between 102.5 in the morning to 103.5 in the afternoon until May 9, then it dropped to subnormal. The spots remained dark until about the 14th, when they became much lighter, gradually disappearing, first from the extremities and back. Recovered.

Treatment: Bowels kept open with calomel. Quinine sulphate 2.6 grams by mouth every twenty-four hours, and quinine hydrochlorate in gradually increasing doses up to 3.3 grams every twenty-four hours hypodermically until improvement began, then gradually decreased. Patient was frequently given hot sponge baths, which allayed the restlessness and lessened the congestion of the skin, causing spots to change from dark red to rosy red.



## CASE 119, 1903.

R. S., female, age 5 years, residence 1 mile north of Florence and about one-eighth mile south of O. G.'s residence. (Map, p. 8, case No. 91, 1902.) Child's two sisters and brother had been frequently bitten by ticks during the spring of 1903. This child had, however, been in Missoula during most of the spring until three weeks before sickness began. The wound remained sore and some pain and swelling was present, extending down side of head behind ear and to right neck.

April 25 patient appeared dull and feverish. On April 27 spots began to appear first on back and thighs (child had been in bed since April 25). Dr. Bryce, of Stevensville, saw patient on this day (April 27). Temperature 102. Quinine hydrochlorate was given by mouth and room darkened. Patient seen April 29, 12 m., by Drs. Bryce, Johnson, and Wilson. Child feeling well; mind clear. Spots consisted of fine petechiae. Temperature 101, pulse 120, strong and regular. No examination of blood permitted.

Patient examined May 2 by Drs. Bryce, Anderson, and Wilson. Child weaker and more restless than on April 29, otherwise condition much the same. Pulse 120, temperature 101.4. Quinine hydrochlorate was given in 10-grain doses twice daily, at first by rectum. Temperature remained about 102°

On May 5 gradually became unconscious and remained so for about five days, and then gradual improvement began, which was interrupted by an attack of acute indigestion on the 14th, which gradually passed off. Spots remained dark red until about the 12th, and then began to fade. Recovery.

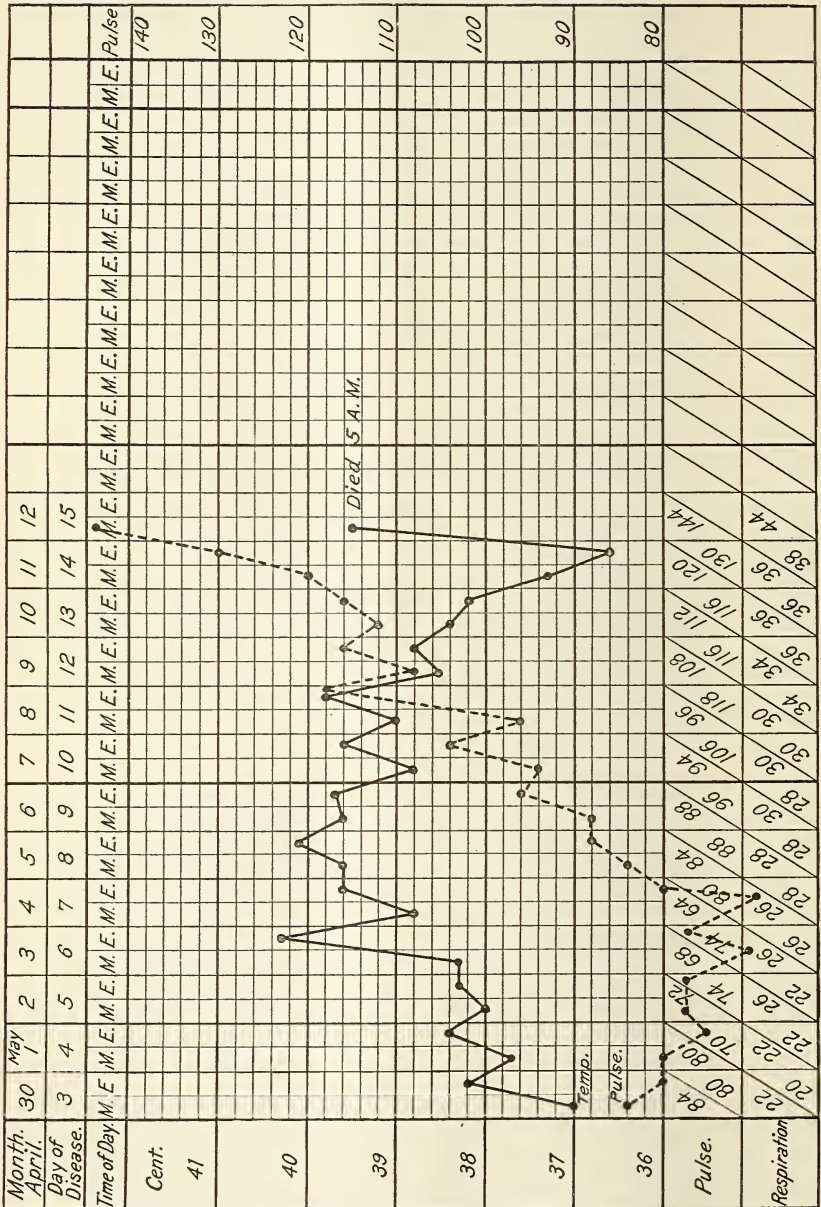
## CASE 120, 1903.

E. M., Finlander, age 28, resident of cottage where O. G., case 91, 1902, died; about 1 mile south and 1 mile west of Florence station. (See map, p. 8.) Had not often been bitten by ticks during the spring of 1903; in fact, does not remember having been bitten at all until he removed two ticks April 28, one from over left breast and the other from over left biceps. These ticks must have been in place for some time, since both were filled with blood.

On the evening of Monday, April 28, patient had a chill, followed by fever and pains in back and limbs. Pains and fever continued next day and patient walked to a friend's  $1\frac{1}{4}$  miles distant. On arrival there he examined himself and found the two ticks above mentioned.

On April 29, 3 p. m., patient first seen by Dr. Bryce. Temperature 102.5, pulse 108, furred tongue, peculiar, sweetish odor of breath, circulation on compressed areas and extremities feeble. Mottling of skin over palms of hands, especially thumbs. Patient showed considerable mental dullness and complained of headache, pains in back

and limbs, and bad taste in mouth. Diagnosis of beginning spotted fever was made. Patient given 15 grains of blue mass and 40 grains of quinine hydrochlorate by mouth.



Name, E. M.; case, 120; age, 28; disease, tick fever.

On the morning of April 30 patient was brought to St. Patrick's Hospital and placed under the care of Dr. Mills. (For temperature, pulse, respiration, etc., from this time see chart.)



Symptoms as noted by Dr. Bryce continued after initial slight abatement until May 4, when patient felt worse. On the morning of May 5 Dr. Mills observed small red spots on right side over region of liver; more spots on back and on wrists in the afternoon. On the morning of May 6 spots were quite abundant over regions noted above and also over thighs and forearms. Specimens of blood taken, fixed, and stained by Dr. Charles Pixley showed a few intracellular bodies.

At 3 p. m., May 6, patient was examined by Drs. Mills, Pixley, Ashburn, Merritt, Anderson, and Wilson. Patient apathetic; tongue with heavy, white coat, red margins and tip. Spots were numerous on extremities and back; few or almost absent over abdomen; scattered, but larger and more plentiful, over chest; obscured on face by tan, beard, and pockmarks. Spots were 2 to 5 mm. in diameter, rosy in color, not elevated, and disappeared readily on pressure, also readily reappeared when pressure was removed. Spleen much enlarged; liver normal. Considerable gurgling and tenderness in right iliac fossa. Fresh blood showed a very few organisms in red cells, mostly of small type. Count gave—

Red blood corpuscles .....	4,744,000
Leucocytes .....	4,800
Hemoglobin .....	per cent.. 90

Examined again 10.30 a. m. May 7, 1903, by Drs. Mills, Pixley, Bryce, Anderson, and Wilson. Spots more general over body, but somewhat lighter in color than on previous day. Patient feeling better. Spleen and liver as on previous day. Gurgling in right iliac fossa still present; no tenderness. Fresh blood showed a few organisms, mostly of small type.

Red blood corpuscles .....	4,722,000
Leucocytes .....	6,900
Hemoglobin .....	per cent.. 87

Patient seen on the 8th of May, 10 a. m., by Drs. Mills and Anderson. Patient sleeping, having had sulphonal, grains 40, the night before. Conjunctivæ much injected. Spots bright red, very numerous on back, plentiful on legs, thighs, arms, and especially on forearms; disappear very slowly on pressure and return slowly. Spleen and liver as yesterday; pulse of fair volume.

Red blood corpuscles .....	4,721,000
Hemoglobin .....	per cent.. 85

Very few intracellular bodies seen in fresh blood preparations. Small amount of albumin in urine, heavy deposit phosphates; no casts or red blood cells.

May 9, 1903, patient seen by Drs. Mills, Wilson, and Anderson. Apparently not as well as yesterday. Conjunctivæ much injected.

Spots on back bright red, do not disappear on pressure; on arms and lower limbs disappear very slowly and return slowly.

Red blood corpuscles.....	4,458,000
Hemoglobin.....per cent..	82

Few intracellular bodies seen in fresh blood in red cells. Paired organisms, united by fine threads in two cells, seen for the first time. Albumin present; granular and epithelial casts.

May 10, 1903, 11 a. m., patient seen by Drs. Mills, Wilson, and Anderson. Much weaker than yesterday. Had nosebleed during night. Pulse about 102 and of poor volume. Spots on back of a petechial character and do not disappear on pressure; on hands and legs disappear very slowly.

Red blood corpuscles.....	3,858,000
Hemoglobin.....per cent..	77

Many intracellular bodies seen in fresh preparations. A few paired ones united by fine thread.

May 10, 1903, 8 p. m., patient seen by Drs. Mills and Anderson. Pulse stronger and fuller than this morning. Had nosebleed for about thirty minutes in afternoon and morning.

May 11, 1903, patient seen by Drs. Mills, Wilson, and Anderson. Very much weaker. The conjunctivæ much injected and jaundiced. Pulse about 120; very poor volume. Spots on back distinctly petechial and dark purple; on hands and lower limbs petechial in character; dark spots on hands; skin distinctly yellow.

Red blood corpuscles.....	3,672,000
Hemoglobin.....per cent..	75

Albumin present in urine; granular and epithelial casts; no red cells. Blood taken on the 12th day of the disease did not give positive widal reaction with *B. typhosus* in a dilution of 1:20.

Patient died May 12 at 5 a. m. At 6 a. m. was removed to undertaking rooms, surface of body cleaned and sponged with embalming fluid (formaldehyde). Autopsy at 2 p. m. by Drs. Anderson and Wilson, in presence of Drs. Mills, Pixley, Gwinn, Spottswood, and Olson.

Body that of a well-nourished man. Panniculus adiposus about normal. Some edema about ankles, hands, and face. Rigor mortis not intense. Small to large petechial hemorrhages covering body, somewhat obscured by tan on face and hands, and by thickened skin of hands and feet. Petechial spots over chest and abdomen from pin point to 5 mm. in diameter. Over dependent portions of elbows, thighs, and back areas are largest, being from 1 to 3 cm. in diameter. Over inner aspect of arm and forearm petechial spots are very thick-

set, but not coalescent. The epidermis over the scrotum was sloughed off from area about 2 to 5 cm. in diameter. On the left chest 3 cm. from middle line and just above the left biceps were two small recent scars. (See history of tick bite.)

Post mortem lividity on dependent portions of skin and thighs. Entire skin deeply jaundiced.

Lungs: There was no adhesion of the pleura. Lungs were normally inflated, containing no consolidated areas except a very few points resembling emboli.

Pericardium: Normal; cavity contained about two ounces of fluid. Right heart half filled with blood; left contracted. Small chicken-fat clots in auricles. A few small hemorrhages over left ventricle near inter-ventricular groove under the pericardium. Myocardium somewhat pale and flabby.

Endocardium apparently normal.

Spleen: Greatly enlarged (weight, 20 ounces) one hour after removal; very soft, dark, and diffluent.

Stomach: Apparently normal, except hypostatic congestion over dorsal surface of fundus.

Small intestine: Empty and showing no inflammation or congestion except hypostatic. Peyer's patches pale and not congested.

Mesenteric and retroperitoneal glands pale and not enlarged.

Liver: Enlarged (weight, 92½ ounces) one hour after removal. Pale, fatty in appearance, and in some areas outlined by engorged bile ducts.

Pancreas: Normal in appearance, except enlargement (weight 5 ounces), one hour after removal.

Kidneys: Enlarged. Weight of left 10 ounces one hour after removal. Capsule adherent; minute subcapsular hemorrhages, especially over greater curvature. On section, cortex congested; pyramids well outlined. Small hemorrhages about 1 mm. in diameter in pelvis.

Bladder wall: Apparently normal; cavity contained about 4 ounces of urine.

Cultures in broth and on Löffler's serum were made from pericardial fluid, heart's blood, spleen pulp, liver and kidney substance. Smear preparations were made from lung substance, heart wall, spleen pulp, liver and kidney substance, and red marrow of rib. Portions of skin, lung, heart wall, spleen, liver, small intestine (including Peyer's patches), pancreas, and kidneys were preserved in Zenker's fluid, 95 per cent alcohol and 10 per cent formalin. Portions of rib were fixed in picro-sulphuric and nitro-sulphuric acid solutions.

*Cultures.*—After forty-eight hours in the incubator all cultures remained sterile, except one from the liver and one from the kidney. The serum culture from the liver developed one colony of a staphylococcus, which remained white after seventy-two hours' growth (presumably *Staphylococcus pyogenes albus*).

On the serum culture from the kidney there developed a few colonies of a small bacillus which in broth, on serum, plain agar, and in and on litmus dextrose agar gave the appearance and the reaction of *Bacillus coli. c.*

CASE 121, 1903.

Mrs. L. M., age 30, born in Germany, residence near Rock Creek clubhouse. (See map, p. 8.) Mother of child H. M., case 107, 1902.

Had not been away from home since October, 1902, and there had been no visitors at the house since last fall; husband had not been to Missoula since winter. These details are mentioned to show the isolation of the locality and the impossibility of infection from the Bitter Root Valley.

Two months pregnant. Had been in good health for past year and spent considerable time shooting near home and clubhouse during the spring. All the members of family had been frequently bitten by ticks during spring of 1903. As soon as ticks were discovered they were removed by ammonia or whisky, and lately by applying carbolic acid.

On May 3 a tick was removed from patient over left breast and another over left scapula; ammonia only was used.

On May 10 she complained of headache, backache, and nausea; went to bed for a few hours.

May 11, had a distinct chill, followed by considerable fever.

May 12 and 13, felt better in morning but worse in evening.

May 14, confined to bed and Dr. Parson called, but he was unable to go, and Dr. Brown went on the 15th. He found the patient with temperature of 103°, pulse 120, suffering with severe pain in back and limbs, tongue with a heavy white coat; nausea. A few small red spots were noticed on ankles, legs, and knees; none on face or chest; few on anterior aspect of wrists.

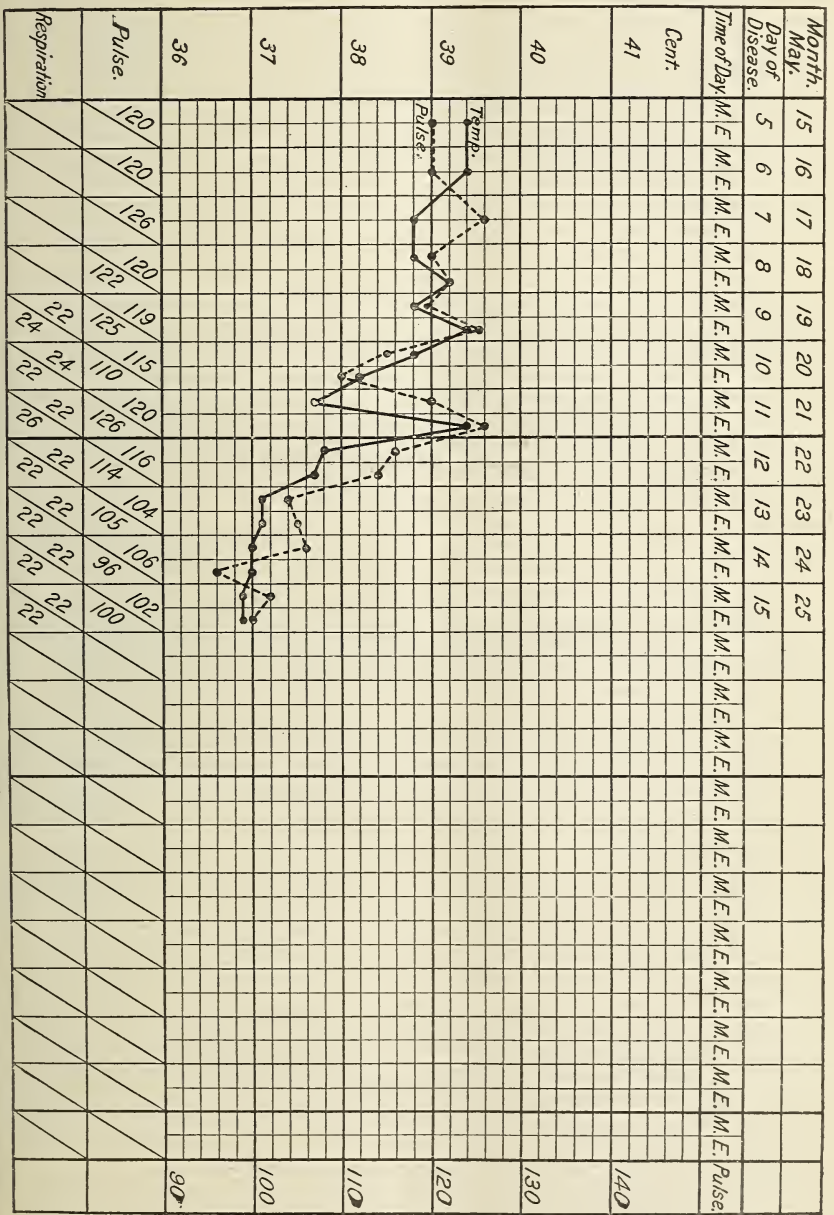
May 16, temperature 103°, pulse 120, spots beginning to appear on back and arms.

May 17, patient brought to Missoula and placed in Dr. Parson's private hospital. Seen at 8 p. m. by Drs. Brown, Wilson, and Anderson. Temperature 102°, pulse 126, full and strong. Headache, backache, soreness of muscles of legs and arms. Tongue with white coat in center and red tip and edges. Small scattered red spots, most plentiful on thighs and back, none on face, few on chest, a very few



on abdomen, some on forearm, wrists, and ankles; all disappear readily on pressure and return quickly when pressure is removed.

May 18, seen at 9 a. m. by Drs. Brown, Wilson, and Anderson.



Name, Mrs. M.; case, 121; age, 30; disease, tick fever.

Had morphine sulphate, one-fourth grain, during night. Condition much as yesterday. Spleen enlarged and easily palpable; liver not enlarged. Spots bright red in color, and more distinct than before;

no increase in number. Conjunctivæ injected. No Kopliks spots. Fresh blood showed few amœboid oval bodies in red blood cells. Count gave—

Red blood corpuscles .....	4,380,000
Leucocytes.....	7,000
Hemoglobin.....per cent..	75

Differential white count gave—

	Per cent.
Polymorphonuclear leucocytes .....	78.7
Large mononuclear leucocytes .....	10.6
Small lymphocytes.....	9.9
Eosinophiles .....	.8
Total .....	100.0

May 19, seen at 9 a. m. by Drs. Brown, Wilson, and Anderson. Dull aching pains in head and back; muscular soreness more marked. Mind clear, slight nausea, constipated. Spots darker in color, but not increased in number; disappear slowly on pressure and return slowly when pressure is removed.

Red blood corpuscles .....	4,723,000 (?)
Leucocytes .....	10,400
Hemoglobin .....	70

Fresh blood shows a few intracorpuseular organisms of the single oval form. A preparation stained with Wright's stain, followed by Löffler's methylene blue, showed a large single oval parasite in a red cell.

May 20, visited at 9 a. m. by Drs. Anderson and Wilson. Headache and muscular soreness more intense. Complains of pain in bones and joints. Had nose bleed during the night. Conjunctivæ congested and slightly jaundiced. Mind clear.

Red blood corpuscles .....	4,452,000
Leucocytes.....	8,400
Hemoglobin.....per cent..	66

Not as many organisms found in fresh blood. No albumin or casts in urine.

May 21, seen by Drs. Anderson and Brown. Complains of ringing in ears. Headache and muscular soreness. Pulse good volume. Spleen about 1 inch below lower border of ribs. Liver slightly enlarged. Spots rather brighter in color than yesterday. Blood examination not permitted. No albumin or casts in urine.

May 22, visited at 9 a. m. by Drs. Brown, Chowning, and Anderson. Had slept fairly well during night. Felt better. Temperature lower. Conjunctivæ more congested and jaundiced. Nosebleed for



short time during the night. Spots brighter in color. Pulse good volume.

Red blood corpuscles .....	4,220,000
Hemoglobin.....per cent..	60

No albumin in urine.

May 23, seen at 9 a. m. by Drs. Brown and Anderson. Says she feels much better; slept well; wants to eat. Bowels moved naturally during night. No pain in head or back. Spots bright, but still do not disappear on pressure. Temperature 99°, pulse 104.

Red blood corpuscles .....	3,772,000
Hemoglobin.....per cent..	62

No albumin in urine.

May 24, visited at 9 a. m. by Drs. Brown, Anderson, and Chowning. Says she feels all right. Spots bright red and a few disappear slowly on pressure. On account of disappearance of tan on face a few were noticed there for the first time. Conjunctivæ still jaundiced.

May 25, seen at 9 a. m. by Drs. Brown and Anderson. Says she is hungry; feels stronger; slept well. Normal temperature for first time.

Red blood corpuscles .....	4,200,600
Hemoglobin.....per cent..	62

Spots beginning to fade. Patient was visited by Drs. Brown and Anderson until May 30, but other than the gradual return of strength and slow disappearance of the spots and jaundice, nothing was noted.

No further blood examinations were permitted after the 25th. Blood taken on the seventh and twelfth days of the illness did not give positive Widal reaction in a dilution of 1:20.

Treatment: On admission a cathartic was given and bowels were kept open each day with medicine or enema. On May 17 treatment was given of calcium sulphide, and, at the suggestion of Drs. Anderson and Wilson, quinine sulphate (2.6 grams) every twenty-four hours was given and continued until recovery. The room was kept dark and warm sponge baths given about three times daily. These seemed to act especially well in relieving the congestion of the skin and allaying restlessness, and after each bath it was noted that the spots lost their dark appearance and became much brighter. The patient was allowed milk, broths, egg-nogs, and occasionally soft toast.

## MORBID ANATOMY.

The following summary of the post-mortem appearances of the disease are based on the findings in seven cases from the Bitter Root Valley.

*Rigor mortis.*—Usually intense and appears early.

*Skin.*—Jaundiced, sometimes deeply. One or more wounds apparently caused by tick bites usually present. The skin has a marbled appearance, well shown by the cut on page 23. On the non-dependent parts of the body spots, petechial in character, from bright red to dark purple in color and from 1 to 3 cm. in diameter; most abundant on wrists, ankles, arms, and back. The capillaries are congested; minute extravasation in the rete extending into the stratum mucosum.

*Nervous system.*—The cerebral and spinal meninges are normal except for slight hypostatic congestion. No increase in fluid. The brain and spinal substance normal.

*Respiratory organs.*—Pleuræ normal and do not contain excess of fluid. Lungs show hypostatic congestion; occasionally pneumonia.

*Circulatory system.*—Pericardium normal. A few small petechial hemorrhages under the epicardium over left ventricle were constantly found. The heart muscle is flabby, softened, and pale. Right heart full of blood; left, contracted and empty. The nuclei are faintly stained; fibers granular and fragmented.

*Digestive organs.*—Stomach normal. Small and large intestines normal in appearance throughout; Peyer's patches rather pale in color. Mesenteric and retroperitoneal glands not enlarged. Spleen usually dark purple in color, soft, diffuent, and from three to four times its normal weight; vessels engorged with blood; many mononuclear leucocytes containing from one to four red corpuscles; no free pigment. Liver enlarged, fatty, and in portions areas outlined by bile pigment; sections usually show an advanced degree of fatty infiltration; bile capillaries full. Pancreas about twice its normal weight.

*Kidneys.*—Enlarged; capsule usually not adherent. Small subcapsular hemorrhages on ventral surface. On section, congested and swollen cortex; pyramids well outlined and deep red color. Small hemorrhages in pelvis. Microscopically there are minute extravasations of blood in cortex and under the capsule: veins filled with blood. Nuclei of the convoluted tubules stain poorly; cells granular and in some places detached; newly formed casts in tubules. Bladder normal and usually with small amount of dark urine.

## PROGNOSIS.

Of 121 cases which have occurred in or near the Bitter Root Valley, 84 died, giving a case mortality of about 70 per cent. The mortality varies within narrow limits from year to year, some years as many as

90 per cent of those attacked dying. The cases which have occurred near Bridger, Mont., show about the same mortality. Death usually occurs between the sixth and the twelfth day. The abundance of the eruption apparently bears no relation to the severity of the disease. The disease in Nevada and Idaho is not nearly as fatal as in Montana. Dr. Maxey says of the Idaho cases:

The prognosis in spotted fever is, as a rule, very favorable if the patient is transferred to the lower valleys where he can have home comforts and proper care. The disease seems to be more malignant in some localities than it is in others, and in one year than in another.

#### DIAGNOSIS.

Cases occurring in the infected localities and presenting a history of tick bites, chill, pain in head and back, muscular soreness, constipation, macular eruption, first on the wrists and ankles, appearing on the third day of illness, becoming petechial in character, do not present much difficulty in diagnosing spotted (tick) fever. A blood examination should be made in all suspicious cases. There are five diseases which might cause some difficulty in differentiating them from spotted fever.

#### DENGUE.

This is a disease of tropical and subtropical countries, whereas spotted fever occurs at an elevation of from 3,000 to 4,000 feet above sea level. The swollen joints, pleomorphic eruption over the joints, never petechial, apyretic period, and short course of the disease would differentiate it from spotted fever.

#### CEREBRO-SPINAL MENINGITIS.

The stiffness of the muscles of the neck, photophobia, sensitiveness to sudden noises, headache, and rigidity of the muscles of the back and neck, with the not altogether constant irregularly situated rash, should not cause much trouble.

#### PELIOSIS RHEUMATICA.

In this disease the sore throat, multiple arthritis with purpura and urticaria, and comparative rarity of the disease, offer a sufficiently distinct clinical picture.

#### TYPHOID FEVER.

Clinically this disease closely resembles spotted fever, but the rose spots appearing first on the abdomen—papular in character—diarrhea, Widal reaction, and presence of the typhoid bacilli in cultures from the blood of typhoid fever, and the presence of parasites in the red blood cells of spotted fever, suffice to separate distinctly the two diseases.

## TYPHUS FEVER.

Spotted (tick) fever, I think, more closely resembles typhus fever than any other disease, and cases of typhus fever occurring in a locality in which spotted fever prevails would, without a blood examination and close bedside observation, cause much trouble in diagnosis. In typhus we have the longer period of incubation, absence of a history of tick bites, the eruption which first appears on the abdomen and chest, its intensely contagious character, especially prevalent in the winter months, not limited to a short time in the spring, and marked nervous symptoms. As before mentioned, two cases of spotted fever have never been known to occur in the same family the same season, thus conclusively showing the noncontagious character of the disease.

## TREATMENT.

Until the past season the treatment of the disease has been purely symptomatic, but after the discovery of the parasite Dr. Wilson and the writer suggested the use of quinine in large doses, preferably hypodermatically. In five cases in which it was used systematically and in large doses the results were most happy, all recovering. Five cases which did not have the treatment died. Of course, 10 cases is too small a number on which to base very positive conclusions, but I hope that the use of quinine will be followed in the future treatment of the disease.

Quinine bimuriate, 1 gram, should be given hypodermatically every six hours. If there is great objection to the use of the needle, the sulphate, 1 gram, every four hours may be given by mouth; but the irritable condition of the stomach at times may prevent. The use of quinine should be begun as soon as the diagnosis is made and persisted with in decreasing doses as convalescence begins.

Some of the valley physicians seemed to fear that quinine depressed the heart and caused nervous symptoms; but I am of the opinion that the great good the drug does more than counterbalances these effects. I strongly advise the early and continuous use of large doses of quinine.

Some physicians speak well of calcium sulphide, and others of creosote.

The heart should be supported with strychnine, whisky, or other appropriate cardiac stimulants.

For the severe pain in the head and back during the first week Dover's powders or morphine sulphate may be used. The patient should be encouraged to drink large quantities of water to flush out the kidneys. For the fever, warm sponge baths or packs are useful and refreshing to the patient. After a bath the spots lose their dark



color and become much brighter. The room should be kept dark and as free from noise as possible.

Milk, buttermilk, broths, soft eggs, and soft toast may all be allowed. The whisky may be administered in an eggnog.

As soon as a person is bitten by a tick the insect should be removed and the place cauterized with 95 per cent carbolic acid. There is sometimes difficulty in removing the tick; but by applying ammonia, turpentine, kerosene, or carbolized vaseline it can usually be detached without trouble.

The disease, considered from a public-health standpoint, is of much greater importance than was thought until recently. On account of its high mortality in the Bitter Root district attention has been focused there, but on investigation the disease was found to be spread over a large area. The mortality, for some unknown reason, is greatly higher in Montana than in the other States. The disease is not much dreaded in Idaho or in Nevada, but the terror it excites in the Bitter Root Valley is great. If, as seems very probable and almost proved, the tick is the means by which the disease is spread, the question of the prevention of the disease resolves itself into the destruction of the ticks. This is an almost impossible task over such a large area, especially of such varied topography. When conditions will permit, burning the undergrowth and stubble will be an effective method for the destruction of ticks. This may be done either in the early fall or preferably in the early spring, when the ticks are just beginning to move about.

## PLATE I.

Drawn with Abbe drawing camera. Stained with Wright's stain, followed by Loeffler's blue.  $\times 750$ .

Fig. 1. Small form of the parasite found in one field.

Fig. 2. The same, another field.

Fig. 3. Showing parasite with central stained spot surrounded by vacuole.



*Fig. 1.**Fig. 2.**Fig. 3.*





## PLATE II.

Fresh blood drawn with Abbe drawing camera.

Figs. 4 and 5. Small form of the parasite.  $\times 665$ .

Fig. 6. Large form.  $\times 665$ .

Figs. 7 and 8. Single form of the parasite.  $\times 1,000$ .

Fig. 9. Double form of the parasite.  $\times 1,000$ .

Fig. 10. One field showing two infected corpuscles.  $\times 665$ .

Fig. 11. One field showing a corpuscle with a large and small parasite.  $\times 1,000$ .



Fig. 4.



Fig. 5.



Fig. 6.



Fig. 7.



Fig. 8.



Fig. 9.

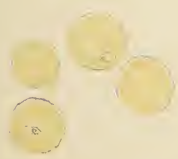


Fig. 10.



Fig. 11.







## APPENDIX.

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### A REPORT OF TWO CASES OF "SPOTTED FEVER."

By DR. G. A. GATES,  
*Bridger, Mont.*

#### CASE I.

On May 29, 1898, I was called to see L. M., at Thermopolis, Wyo. Patient was a male, white, aged 23 years, sandy or red hair, rather spare built; had come from Iowa about three months previous to present attack. He became ill while traveling overland from Lander to Thermopolis, Wyo. Having camped out several nights during the journey, on one or two occasions his bedding became thoroughly wet from the heavy rains of that season.

When first seen patient's face was deeply flushed, eyes bright, skin hot and dry, with a beginning petechia on the forehead, back of hands, wrists, and ankles. Headache, thirst, slightly sore throat, and a soreness of muscles and aching throughout the body were complained of by the patient. Temperature  $104^{\circ}$  F., pulse 120, urine highly colored, no albumin. Complete loss of appetite; no other gastro-intestinal symptoms.

Patient was given small doses of aconite and spirit of nitrous ether and small doses of alcohol until fever was reduced and bowels moved freely.

This was followed by a prescription containing salol, hydrate of chloral, with soda bicarbonate, caffeine citrate, and pepsin, combined in a powder and given every four or six hours. Patient was sponged with cool or cold water, as needed for high temperature, and placed on a diet of milk, gruel, raw eggs, and whisky.

The fever ran an irregular course, with great variation, reaching at times a temperature of  $104.5^{\circ}$  F. and again sinking to  $97^{\circ}$  F. This low temperature was observed during the last of the first week of the disease, at which time patient was in a state of collapse, being almost pulseless and having a hard chill at the time.

Slight albuminuria appeared during the second week.

Delirium was very slight; patient could be aroused at any time.

Fever gradually subsided after eighteen days.



LEUCODERMIA (LEUCODERMIA)



The petechiæ increased in size and number very rapidly during the first two weeks, forming large, irregularly shaped spots from the size of a little finger nail to spots one-half by one-half inch in size. These spots darkened in color, becoming bluish, with a surrounding yellow tinge. The spots were slow in disappearing, some traces of them being visible seven months after recovery.

#### CASE 8.

Mrs. H., white, aged 67 years, was bitten by a tick May 4 and 8, the tick being removed from the left thigh on May 8, 1903. The species of ticks to which this one belonged is said to have been brought to this section of country by sheep from Bozeman or vicinity. This tick is recognized by having a grayish or whitish spot on the back of the head. The tick which bit patient came from near the mouth of Dry Creek, on the west side of the Clarke Fork River, 7 miles south of Bridger.

Patient first complained of feeling ill on May 9. She complained of headache, tired feeling, general soreness of the muscles, and loss of appetite.

I saw patient first May 11. Temperature 103, pulse 104, cheeks flushed, tongue white coat on sides, rather dry. Quite severe headache and tired feeling were the only subjective symptoms. Urine dark; on examination showed slight amount of albumin and some hyaline and granular blood casts and numerous bacteria; the quantity for following twenty-four hours was 32 ounces; the quantity gradually diminished from this time until two days before death, when there was complete anuria. Red and white blood cells, with an enormous number of granular, blood, and epithelial casts, were present in last samples of urine obtained.

During the 12th and 13th temperature varied from 101 to 103.5 F. On the 14th it rose to 104.4, slowly dropping to 101 on the morning of the 17th, where it remained until death.

Food and medicine were taken well until the last thirty-six hours. Vomiting occurred once. A number of watery evacuations were produced by the action of elaterium.

Rectal and subcutaneous injections of normal saline solution were given. The combined use of the above and hot packs, together with hot elder water and liquor ammonii acetatis internally, produced only slight diaphoresis, and that mostly about the head.

On the 15th petechial eruption began to make its appearance upon the buttocks, back, and thighs. These increased in number and size until every portion of the body was covered, though but little showing on the face. They seemed to be subcutaneous or intracutaneous extravasations of blood, rapidly darkening in color.



There seemed to be a profound impression on the nervous system from the very first symptoms of the disease. Muttering delirium, and a semicomatose condition, from which the patient could be roused only with much effort, were early and prominent symptoms.

Respiration varied from 30 to 40 per minute throughout the course of the disease and continued until after all signs of heart action had ceased.

Highest pulse rate observed was 186 per minute.

Patient died on the morning of May 19 about 1 a. m.

This case was also seen by Dr. Johnson, of this place, and Dr. Lutz, of Red Lodge, in consultation with me.

TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 15.

M. J. ROSENAU, Director.

July, 1903.

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INEFFICIENCY OF FERROUS SULPHATE  
AS AN ANTISEPTIC AND  
GERMICIDE.

BY

ALLAN J. McLAUGHLIN.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.  
1903.

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The following *bulletins* [Bull. Nos. 1-7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

- No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.
- No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.
- No. 3.—Sulphur dioxide as a germicidal agent. By H. D. Geddings.
- No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.
- No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.
- No. 6.—Disinfection against mosquitoes with formaldehyd and sulphur dioxid. By M. J. Rosenau.
- No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

By act of Congress, approved July 1, 1902, the name of the "United States Marine-Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.

Since the change of name of the service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:

- No. 8.—Laboratory course in bacteriology and pathology. By M. J. Rosenau.
- No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.
- No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or ancylostomiasis) in the United States. By Ch. Wardell Stiles.
- No. 11.—Experimental investigation of *Trypanosoma Lewisii*. By Edward Francis.
- No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.
- No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis*; by Ch. Wardell Stiles.
- No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.
- No. 15.—Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allan J. McLaughlin.

In citing these bulletins, beginning with No. 8, bibliographers and authors are requested to adopt the following abbreviations: Bull. No. —, Hyg. Lab., U. S. Pub. Health & Mar.-Hosp. Serv., Wash., pp. —.

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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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BY

ALLAN J. McLAUGHLIN.



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## ORGANIZATION OF HYGIENIC LABORATORY.

WALTER WYMAN, *Surgeon-General,*  
*United States Public Health and Marine-Hospital Service.*

### ADVISORY BOARD.

Major Walter D. McCaw, Surgeon U. S. Army; Surgeon John F. Urie, U. S. Navy; Dr. D. E. Salmon, Chief of U. S. Bureau of Animal Industry; and Milton J. Rosenau, U. S. Public Health and Marine-Hospital Service, *ex officio*.

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# INEFFICIENCY OF FERROUS SULPHATE AS AN ANTISEPTIC AND GERMICIDE.

By ALLAN J. McLAUGHLIN,

*Assistant Surgeon, Public Health and Marine-Hospital Service.*

Ferrous sulphate, green sulphate of iron, green vitriol, or copperas, are the various names of a chemical substance that has long been used extensively for the disinfection of animal excreta. It has been popular among the laity because of its cheapness and ease of application as a disinfectant and deodorant for privy vaults, etc. It has official recognition in the French army as a disinfectant for latrines. The literature upon the subject is scanty and in some instances contradictory.

Chevalier reviewed a paper by Schattenman, read before the Paris Academy of Sciences in 1846, in which Schattenman set forth that 2 or 3 kilograms of ferrous sulphate were necessary to disinfect 100 liters of fecal matter. He laid stress on the fact that an intimate mixture must be made of the fecal matter and ferrous sulphate solution.

Koch found that a 5 per cent solution failed to destroy anthrax spores in six days.

Miquel classes ferrous sulphate as a moderately antiseptic substance. A proportion of 1:90 was required to restrain putrefaction.

Rideal says:

The sulphates are not perceptibly antiseptic. Those of iron, mercury, and some other metals depend for their power on the amount of the base present, and not on the acid.

Bergey says:

It [ferrous sulphate] is not a strong disinfectant, but it is serviceable as a deodorant. It should be used in the proportion of 1 kilogram (dissolved in 10 liters of water) to a cubic meter of the contents of the vault.

Munson says:

The properties of ferrous sulphate which render it useful for purposes of disinfection depend upon its tendency to appropriate oxygen and so become converted into the ferric sulphate. These qualities, however, must be considered as antiseptic rather than disinfectant, since, according to Laveran, the addition of even 5 or 6 per cent of the salt to fecal matter is unable uniformly to affect the sterilization of the latter. Sulphate of iron is used only in solution, the amount of the iron salt to be daily employed depending upon the estimated increment of the fresh fecal matter rather than upon any particular strength of the solution. Should the contents of the latrine be semifluid, the solution of sulphate of iron may with advantage be made up with but a small proportion of water, since for efficiency a high proportion of



ferrous sulphate should be brought into direct contact with the excreta. In practice, a proportion of five parts of the iron salt in each hundred of the total contents of the latrine vault should be considered as essential to efficiency. In the French army ferrous sulphate is much used for the disinfection of latrines in a 10 per cent solution. It is officially laid down that at least 250 c. c. of such a solution should be used per day for each person using the latrine.

Sternberg found that a solution of 20 per cent failed to destroy micrococci and putrefactive bacteria (1883). Later he found that 10 per cent failed to kill pus cocci, but was fatal to micrococcus tetragenous—two hours' exposure. He also found that 1:200 prevented the development of micrococci and of putrefactive bacteria in bouillon placed in the incubator for forty-eight hours.

Jäger<sup>a</sup> found that a solution of 1:3 destroyed the infective virulence of some pathogenic organisms (fowl cholera, rothlauf, glanders), as tested by injection into mice, but failed to kill anthrax spores and tubercle bacilli.

Leitz<sup>a</sup> found that a 5 per cent solution required three days' exposure for the destruction of the typhoid bacillus.

In a series of experiments bearing upon the disinfection of feces, Foote mixed decomposing urine with feces, 1 part feces to two-thirds of its bulk of urine. Five hundred c. c. of the disinfectant mixture (ferrous sulphate  $\bar{5}$  xviii, water 1 gallon) was added to 250 c. c. of the feces-urine mixture and the two thoroughly mixed. Inoculations of one platinum loopful were made from the mixture into gelatin and bouillon after one hour, four hours, and forty-eight hours of action. The sulphate of iron solution had little if any effect. Even after forty-eight hours' action the colonies upon the gelatin plates were innumerable and a profuse growth appeared in the bouillon tubes.

In order to ascertain the antiseptic and disinfectant value of ferrous sulphate a number of experiments were carried out with the results shown in the following tables:

ANTISEPTIC POWER OF FERROUS SULPHATE.

TABLE I.

Bouillon with the addition of ferrous sulphate in various percentages contaminated by the addition of a small quantity of garden earth. Kept at room temperature.

Proportion of ferrous sulphate.	First day.	Second day.	Third day.	Tenth day.	Twenty-first day.
1:200 .....	Very foul odor.....	.....	.....	.....	.....
1:150 .....	.....do.....	.....	.....	.....	.....
1:100 .....	.....do.....	.....	.....	.....	.....
1:50 .....	Foul odor.....	Very foul odor.....	.....	.....	.....
1:40 .....	No odor.....	No odor.....	Foul odor.....	.....	.....
1:30 .....	.....do.....	.....do.....	.....do.....	.....	.....
1:25 .....	.....do.....	.....do.....	No odor.....	Faint odor.....	Foul odor.
1:20 .....	.....do.....	.....do.....	.....do.....	No odor.....	No odor.
1:15 .....	.....do.....	.....do.....	.....do.....	.....do.....	Do.
1:10 .....	.....do.....	.....do.....	.....do.....	.....do.....	Do.
1:5 .....	.....do.....	.....do.....	.....do.....	.....do.....	Do.

<sup>a</sup>Cited by Sternberg.

TABLE II.

Bouillon with the addition of ferrous sulphate in various percentages contaminated by the addition of a small quantity of garden earth. Kept in the incubator.

Proportion of ferrous sulphate.	First day.	Second day.	Third day.	Fifth day.	Fourteenth day.
1:200 .....	Very foul odor .....	.....	.....	.....	.....
1:150 .....	Foul odor .....	.....	.....	.....	.....
1:100 .....	do .....	.....	.....	.....	.....
1:50 .....	No odor .....	Foul odor .....	.....	.....	.....
1:35 .....	do .....	do .....	.....	.....	.....
1:30 .....	do .....	do .....	.....	.....	.....
1:28 .....	do .....	No odor .....	Foul odor .....	.....	.....
1:25 .....	do .....	do .....	No odor .....	Foul odor .....	.....
1:23 .....	do .....	do .....	do .....	do .....	.....
1:20 .....	do .....	do .....	do .....	No odor .....	No odor.

## GERMICIDAL ACTION OF FERROUS SULPHATE.

Forty-eight hour bouillon cultures of *B. typhosus*, *B. coli communis*, *B. pyocyaneus*, *vibrio cholera Asiat.*, strong aqueous suspensions from forty-eight hour cultures on agar of *B. anthracis*, *B. subtilis*, *Staphyl. pyog. aureus* and *albus*, and a strong suspension of a forty-eight hour growth of *B. diphtheria* on blood serum were used to contaminate slips of filter paper, silk threads, and glass cover slips. After being contaminated by the culture the paper slips, silk thread and cover slips were placed in the incubator until they were almost dry (in the case of anthrax and *subtilis* they were allowed to dry completely), then the disinfecting agent was applied for definite periods, its action stopped by careful washing in sterile water, the slips and threads planted in bouillon and placed in the incubator for forty-eight hours.

TABLE III.—*Infected material, filter paper.*

Organism employed.	Result after application of sat. sol. of ferrous sulphate.					
	5 minutes.	10 minutes.	20 minutes.	30 minutes.	45 minutes.	60 minutes.
<i>B. anthracis</i> .....	+	+	+	+	+	+
<i>B. subtilis</i> .....	+	+	+	+	+	+
<i>B. typhosus</i> .....	+	+	+	+	+	+
<i>B. coli communis</i> .....	+	+	+	+	+	+
<i>B. pyocyaneus</i> .....	+	+	+	+	+	+
<i>Vib. cholera Asiat</i> .....	+	+	+	+	+	+
<i>B. diphtheria</i> .....	+	+	+	+	+	+
<i>Staphyl. pyog. aureus</i> .....	+	+	+	+	+	+
<i>Staphyl. epider. albus</i> .....	+	+	+	+	+	+

TABLE IV.—*Infected material, silk threads.*

Organism employed.	Result after application of saturated solution of ferrous sulphate.					
	5 minutes.	10 minutes.	20 minutes.	30 minutes.	45 minutes.	60 minutes.
<i>B. anthracis</i> .....	+	+	+	+	+	+
<i>B. subtilis</i> .....	+	+	+	+	+	+
<i>B. typhosus</i> .....	+	+	+	+	+	+
<i>B. coli communis</i> .....	+	+	+	+	+	+
<i>B. pyocyaneus</i> .....	+	+	+	+	+	+
<i>B. diphtheria</i> .....	+	+	+	+	+	+
<i>Vibrio cholera Asiat</i> .....	+	+	+	+	+	+
<i>Staphyl. pyogenes aureus</i> .....	+	+	+	+	+	+
<i>Staphyl. epider. albus</i> .....	+	+	+	+	+	+

TABLE V.—*Injected material, glass cover slips.*

Organism employed.	Result after application of saturated solution of ferrous sulphate.					
	5 minutes.	10 minutes.	20 minutes.	30 minutes.	45 minutes.	60 minutes.
<i>B. anthracis</i> .....	+	+	+	+	+	+
<i>B. subtilis</i> .....	+	+	+	+	+	+
<i>B. typhosus</i> .....	+	+	+	+	+	+
<i>B. coli communis</i> .....	+	+	+	+	+	+
<i>B. pyocyaneus</i> .....	+	+	+	+	+	+
<i>B. diphtheriæ</i> .....	+	+	+	+	+	+
<i>Vibrio cholera Asiaticus</i> .....	+	+	+	+	+	+
<i>Staphyl. pyogenes aureus</i> .....	+	+	+	+	+	+
<i>Staphyl. epider. albus</i> .....	+	+	+	+	+	+

Some of the pathogenic organisms tested (*V. cholerae* and *B. typhosus*) did not grow after one hour exposure to the iron solution: but in the following experiments upon feces it will be seen that *V. cholerae* was recovered from feces after forty-eight hours exposure to a saturated solution. In the experiments upon feces the saturated solution of ferrous sulphate constituted twice the bulk of the feces and was intimately mixed with it, and all lumps broken up to make as nearly as possible a homogeneous mixture.

TABLE VI.

Twenty-five grams of feces thoroughly mixed with twice its bulk (50 c. c.) of a saturated solution of ferrous sulphate. At definite intervals a platinum wire loopful was planted in bouillon and placed in the incubator twenty-four hours, with the results given below.

Time of exposure to iron solution.	Result.
5 minutes .....	Good growth.
10 minutes .....	Do.
20 minutes .....	Do.
30 minutes .....	Do.
40 minutes .....	Do.
50 minutes .....	Do.
1 hour .....	Do.
2 hours .....	Do.
18 hours .....	Do.
24 hours .....	Do.
48 hours .....	Do.
72 hours .....	Do.

TABLE VII.

Twenty-five grams feces thinned by the addition of 10 c. c. bouillon culture of *pyocyaneus* and thoroughly mixed with twice its bulk of a saturated solution of ferrous sulphate. A platinum wire loopful of the mixture was planted at definite intervals in bouillon and placed in the incubator for twenty-four hours, with the result indicated below.

Time of exposure to iron solution.	Result.
1 hour .....	Good growth. <i>B. pyocyaneus</i> recovered.
2 hours .....	Do.
3 hours .....	Do.
4 hours .....	Do.
5 hours .....	Do.
6 hours .....	Do.
24 hours .....	Do.
48 hours .....	Do.
72 hours .....	Do.

TABLE VIII.

A mixture of feces, thinned by the addition of 10 c. c. of a twenty-four-hour bouillon culture of *Vibrio cholerae* Asiat. and mixed with twice its bulk of a saturated solution of ferrous sulphate, was tested at stated intervals by taking out a platinum wire loopful and planting in bouillon. The results are indicated below.

Time of exposure to iron solution.	Result.
6 hours .....	Good growth. <i>V. cholerae</i> recovered.
24 hours .....	Do.
26 hours .....	Do.
28 hours .....	Do.
30 hours .....	Do.
48 hours .....	Do.

Sulphate of iron does not show any restraining influence over the development of putrefactive changes unless it constitutes more than 2 per cent of the mixture. It does not permanently restrain the development of putrefactive changes unless it constitutes at least 5 per cent of the mixture.

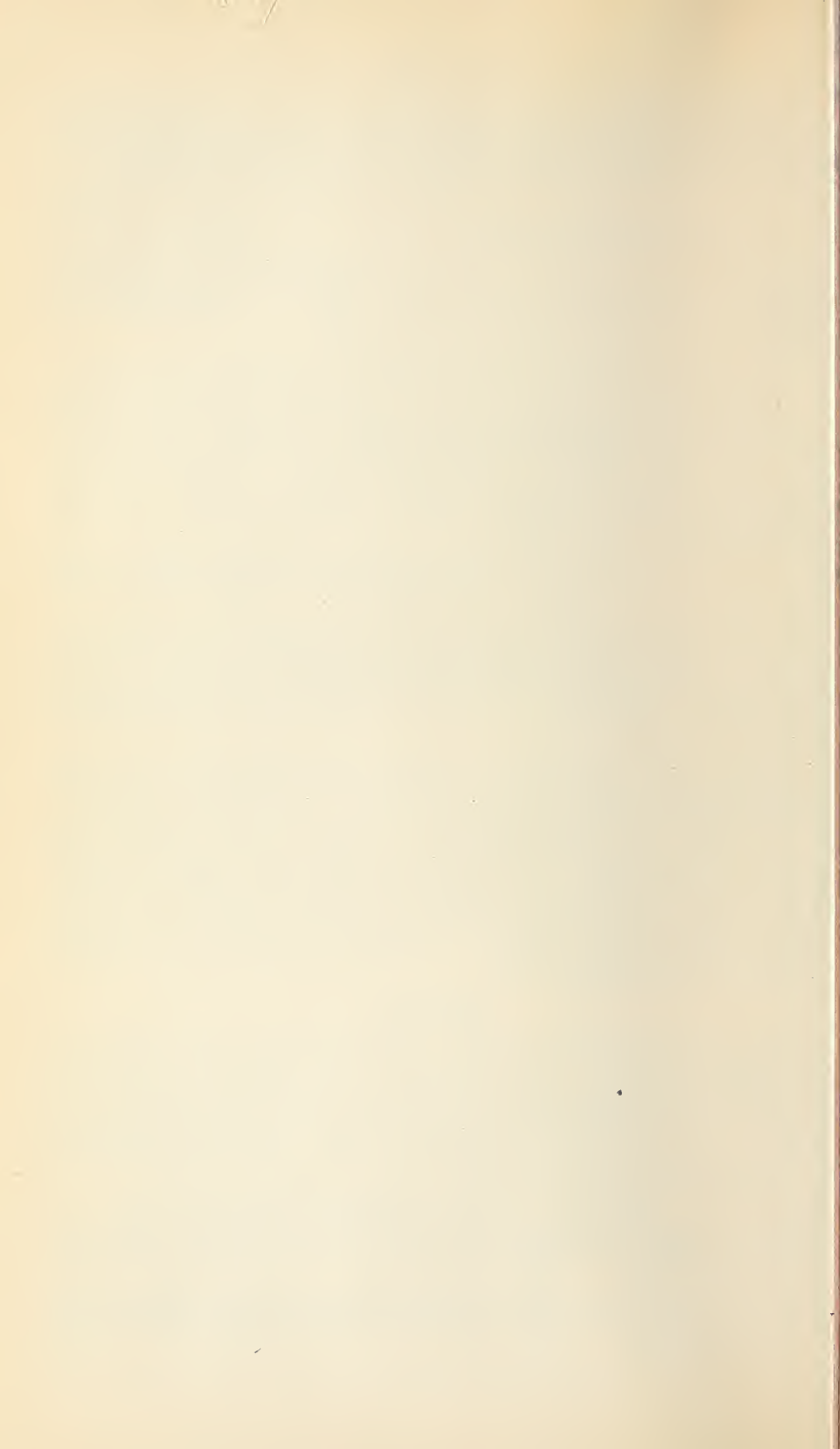
As a germicide it has little or no action, even when applied under the most favorable conditions for disinfection. Where the material to be disinfected was flooded with the agent in saturated solution, in nearly all experiments, its action was not apparent, and it failed to disinfect under such favorable conditions seven different varieties of pathogenic organisms out of nine, after an exposure of one hour to a saturated solution.

Tested upon feces it failed to disinfect after three days, although intimately mixed with the feces, and when it was applied in saturated solution and in double the bulk of the material to be disinfected.

It seems therefore that copperas or sulphate of iron is of no real value as a disinfectant. The strongest solution has either no disinfectant action at all, or its disinfectant action is so slow and uncertain that its demonstration might be a matter of interest, but certainly could not be of practical value.

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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 16.

M. J. ROSENAU, Director

September, 1903.

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# THE ANTISEPTIC AND GERMICIDAL PROPERTIES OF GLYCERIN.

BY

M. J. ROSENAU.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.

1903.



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The following *bulletins* [Bulls. Nos. 1-7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

- No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.
- No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.
- No. 3.—Sulphur dioxide as a germicidal agent. By H. D. Geddings.
- No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.
- No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.
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- No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

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- No. 8.—Laboratory course in bacteriology and pathology. By M. J. Rosenau.
  - No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.
  - No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or ancylostomiasis) in the United States. By Ch. Wardell Stiles.
  - No. 11.—Experimental investigation of *Trypanosoma lewisi*. By Edward Francis.
  - No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.
  - No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis*; by Ch. Wardell Stiles.
  - No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.
  - No. 15.—Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allan J. McLaughlin.
  - No. 16.—The antiseptic and germicidal properties of glycerin. By M. J. Rosenau.
- In citing these bulletins, beginning with No. 8, bibliographers and authors are requested to adopt the following abbreviations: Bull. No. —, Hyg. Lab., U. S. Pub. Health & Mar.-Hosp. Serv., Wash., pp. —.

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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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# THE ANTISEPTIC AND GERMICIDAL PROPERTIES OF GLYCERIN.

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By MILTON J. ROSENAU, Director Hygienic Laboratory, Public Health and Marine-Hospital Service.

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## INTRODUCTION.

In working upon the bacteriology of vaccine virus it became evident that too much confidence was placed in the germicidal value of glycerin. In reviewing the literature upon the subject we were somewhat surprised to learn how meager has been the published work upon this important subject, especially in view of the almost universal practice of using glycerin to prepare and conserve vaccine virus and other organic matter.

Since Copeman, in 1891, devised the method of mixing glycerin with vaccine pulp, much work has been done in studying the effect of glycerin upon the microbial life contaminating bovine vaccine virus, but comparatively little upon the direct action of this interesting substance upon definite pathogenic and saprophytic bacteria. We therefore made a careful study of this question. It has engaged our attention during the odd moments of the past two years, in order to determine precisely the antiseptic and germicidal powers of this important substance. These studies are now published in detail at the request of several vaccine manufacturers, who desire to make practical use of the results obtained.

Our studies were considered under three heads:

(1) We first determined the antiseptic power of glycerin; that is, its property of restraining bacterial growth and the amount required to prevent putrefaction and fermentation.

(2) We determined its exact germicidal value; that is, the amount and time required to destroy pathogenic and saprophytic bacteria, both spore-bearing and nonspore-bearing varieties.

(3) On account of the great importance of tetanus as a contaminator of vaccine virus, we made an extensive series of special studies to determine the effect of glycerin upon the spores of this organism.



## HISTORICAL.

Glycerin was discovered in 1779 by Scheele, a Swedish pharmacist, in the water which came from a simple salve. He gave it the name of "sweet principle of oils."

It is found in a free state, but exists principally in combination with the fatty acids, forming compound ethers, which constitute most of the animal and vegetable solid and liquid fats.

Pasteur showed that it is constantly found in alcoholic fermentation, it being one of the natural constituents of wine, which holds as much as 4 to 7 grams to 50 liters. Beer contains normally 2 to 3 grams per liter. (A. Catillon: *De la glycérine*. Paris, 1903.)

In 1813 Chevreul, in a memorable work, showed that fatty substances on assimilating the elements of water split up into fatty acids and glycerin. This action is brought about by the influence of alkalis, metallic oxides, hydrochloric and sulphuric acids, by water in a closed receptacle at a temperature of  $220^{\circ}$  C. (Berthelot, 1854), superheated steam, and by certain ferments, such as pancreatin (Claude Bernard).

In 1854 Berthelot demonstrated that glycerin is a triatomic alcohol, giving three series of ethers and glycerides.

Several years later Wurtz (1857) made glycerin, by synthesis, by heating on an oil bath at  $120^{\circ}$  to  $125^{\circ}$  C. for eight days tribromopropane, silver acetate, and glacial acetic acid.

## GENERAL USES.

Glycerin is to-day one of the most useful substances, both in the sciences and in the arts. It is used in the preparation of pigments, for the extraction of perfumes from flowers, in lubricating oils, for the preservation of animal matter, such as fresh skins, albumin, vaccine virus, and animal extracts. Its power to protect animal matter against putrefaction, combined with its bland and nonpoisonous properties, renders it an exceedingly important and useful substance.

In pharmacy glycerin has various uses. It is used in making pill masses, in expectorant mixtures, and in the official glycerites (glycerita) of the United States Pharmacopœia.

It is used in paper making, and enters into the composition of inks, beer, wine, soaps, perfumes, toilet waters, cosmetics, and many articles of manufacture, especially explosives (nitroglycerin.)

## PROPERTIES.

Glycerin,  $C_6H_8O_6$  or  $C_3H_4O_3$ , or  $C_6H_5(OH)_3$ , is a colorless, sirupy liquid, without odor, and a sweetish taste. It boils at  $290^{\circ}$  C. at a pressure of 756 mm. and at  $180^{\circ}$  C. in vacuum. Heated with care it evaporates, leaving a residue, and disengages a thick vapor with an insipid but not unpleasant odor. At  $150^{\circ}$  C. it is decomposed by

losing the elements of water into less volatile compounds: Diglycerid ( $C_6H_7O_5$ )<sub>2</sub>, acrolein ( $C_6H_4O_2$ ), acetic acid, carbonic acid, and inflammable gases.

Glycerin should be neutral in reaction.

The density of the anhydrous fluid is 1.269 (1.265, Lyons), but as it is very hygroscopic it can not be kept in this state when exposed to the air without absorbing moisture, and therefore commercially the extreme point of concentration is 1.260, which corresponds to 0.03 to 0.04 per cent of water. The United States and British pharmacopœias require glycerin to have a specific gravity of 1.250; the German pharmacopœia requires 1.225 to 1.235.

Completely deprived of water by several distillations in vacuum, glycerin crystallizes into orthorhombic prisms, having a density of 1.360, fusible at 15° C.

Glycerin is soluble in all proportions in water and alcohol; insoluble in ether, chloroform, benzine, fixed oils, or volatile oils. It dissolves almost all substances soluble in water or in alcohol. Its great affinity for water is one of its best-known properties. Its properties of dissolving albumin and preventing putrefaction have special reference to its use in adding it to vaccine virus.

The number of chemical combinations with glycerin is numerous.

#### PREPARATION.

Glycerin is obtained by decomposing fat into its proximate constituents, either by a caustic alkali, as in the manufacture of soap, or by lead oxide, as in the preparation of lead plaster, or by the action of water at an elevated temperature under pressure. It is purified by distillation.

#### IMPURITIES.

Glycerin is used more or less pure, depending upon the various purposes for which it is employed. It may contain lead, iron, lime as an alkali, or sulphate, carbonate, or chlorid; oxalic, formic, or butyric acid. It is sometimes adulterated with large quantities of water, sugar, glucose, or dextrine, etc. Arsenic is also found in glycerin, particularly that which comes from the manufacture of soap. Glycerin which is obtained by treating stearine with lime is free from arsenic.

#### TESTS FOR IMPURITIES.

A. Catillon (*loc. cit.*, p. 20) gives the following tests for impurities in glycerin:

After testing color, odor, and taste:

1. Reaction must be exactly neutral.
2. Specific gravity, which is an evidence of the watery contents.
3. On heating 10 grams of glycerin over an alcohol lamp it should evaporate without disagreeable odor, without carbonizing, and without leaving a residue.

4. If a residue remains, add to the glycerin some distilled water and several drops of ammonia to determine the presence of lime.
5. A drop of solution of sulphhydrate of soda should not produce a color in glycerin, but throws down a black precipitate if it contains lead or iron.
6. For glucose, treat the glycerin with Fehling's solution, using the usual precautions to obtain the reduction of the copper.
7. The presence of chlorids in glycerin is indicated by silver nitrate. Pure glycerin will show neither opalescence nor precipitates.
8. Tribasic acetate of lead added to glycerin diluted with distilled water produces a limpid solution. A precipitate or a cloudiness indicates the presence of fatty acids.
9. Mix equal parts of glycerin with sulphuric acid. If carbon-dioxid gas is given off it contains oxalic or formic acid.
10. Mix the glycerin with pure alcohol and a little sulphuric acid. An odor of pineapple is immediately developed, due to butyric ether (butyric acid).
11. Glycerin heated to 120° should show no color.
12. For arsenic, test by means of Marsh's apparatus.

#### ACKNOWLEDGMENT.

It is a pleasure to acknowledge the faithful assistance rendered by my assistants in the laboratory in working out some of the details of this study upon glycerin, especially to Drs. John F. Anderson, T. B. McClintic, Allan J. McLaughlin, and Edward Francis.

#### ANTISEPTIC POWER OF GLYCERIN.

The first series of experiments were made in order to determine the antiseptic properties of glycerin; that is, its power to restrain the growth and development of bacteria. This was tested by determining the amount of glycerin necessary to add to nutrient bouillon in order to prevent putrefaction, and the amount necessary to prevent the growth and development of pure cultures of various organisms.

Erlenmayer flasks of 100 c. c. capacity were partly filled with the bouillon-glycerin solution. The flasks were then contaminated with various substances, such as rich, black garden earth, wisps of hay, or fresh stable manure.

The flasks were allowed to remain in a dark corner of the laboratory at room temperature, and results noted.

More or less growth of bacteria and mold was obtained in all the flasks containing 40 per cent of glycerin. Those containing 50 per cent or over remained clear and showed no growth. Therefore, it was plain that the antiseptic power of glycerin lies somewhere between 40 and 50 per cent.

The next series of flasks contained various percentages of glycerin between 40 and 50 and were inoculated in the same way, in order to determine more definitely the exact percentage of glycerin necessary to restrain growth and development of micro-organisms.

*Nutrient bouillon containing various percentages of glycerin (X.), contaminated by the addition of garden earth, and kept in flasks at room temperature.*

Percentage of glycerin.	Day upon which growth appeared.				
	Seventh day.	Eighth day.	Tenth day.	Fifteenth day.	Twenty-first day.
41 per cent.....	Fluid clear; small surface mold.				
42 per cent.....		Small surface mold.			
43 per cent.....		do.			
44 per cent.....		do.			
45 per cent.....			Small surface mold.		
46 per cent.....			do.		
47 per cent.....			do.		
48 per cent.....				Small surface mold.	
49 per cent.....					No growth.

*Nutrient bouillon containing various percentages of glycerin (M.), contaminated by the addition of wisps of hay, and kept in flasks at room temperature.*

Percentage of glycerin.	Day upon which growth appeared.				
	Fifth day.	Sixth day.	Seventh day.	Twelfth day.	Twenty-first day.
41 per cent.....	Feathery growth along course and adherent to straw.				
42 per cent.....	do.				
43 per cent.....		Feathery growth along course and adherent to straw.			
44 per cent.....			Very faint feathery growth along course and adherent to straw.		
45 per cent.....				Very faint growth along course and adherent to straw.	
46 per cent.....					No growth.

*Nutrient bouillon containing various percentages of glycerin (P.), contaminated by the addition of stable manure, and kept in flasks at room temperature.*

Percentage of glycerin.	Day upon which growth appeared.		
	Sixteenth day.	Nineteenth day.	Twenty-first day.
41 per cent.....	Small surface mold.		
42 per cent.....	do.		
43 per cent.....		Small surface mold.	
44 per cent.....			No growth.
45 per cent.....			Do.



*Nutrient bouillon containing various percentages of glycerin (S.), contaminated by the addition of stable manure, and kept in flasks at room temperature.*

Percentage of glycerin.	Day upon which growth appeared.			
	Ninth day.	Tenth day.	Thirteenth day.	Twenty-first day.
41 per cent .....	Small surface mold.			
42 per cent .....		Small surface mold.		
43 per cent .....		Very small surface mold.		
44 per cent .....			Small surface mold.	
45 per cent .....				No growth.
46 per cent .....				Do.

As was to be expected, the exact percentage of glycerin necessary to restrain growth varies within narrow limits with the make of glycerin used and the kind of contamination.

To sum up the antiseptic power of glycerin:

	Per cent.
Glycerin X .....	49
Glycerin M .....	45
Glycerin P .....	43
Glycerin S .....	45
Average .....	45.5

These results do not correspond with Miquel's work in 1884, who found that 225 grams of glycerin in 1 liter of bouillon was sufficient to prevent putrefaction.

The above test having determined the antiseptic power of glycerin against putrefactive changes, another series of experiments was made in order to determine the restraining power of glycerin against pure cultures of various micro-organisms.

The different percentages of glycerin were made as before with nutrient bouillon and this time distributed into test tubes. Each tube was inoculated with a minute but visible portion of the surface growth of the organisms, which were grown for this purpose upon agar slants under favorable conditions, and fresh young cultures were always used to make the inoculation.

The test tubes were incubated at 37° C. and examined daily for growth. In case a growth appeared it was tested for purity. The tubes were observed daily for at least eleven days and the result noted.

As a result of the foregoing experiments glycerin is found to be antiseptic in the following dilutions:

Organism.	Glycerin.				Average percentage.
	P.	X.	S.	G.	
	<i>Per cent.</i>	<i>Per cent.</i>	<i>Per cent.</i>	<i>Per cent.</i>	<i>Per cent.</i>
Staphylococcus pyogenes aureus .....	30	32	33	29	31
Staphylococcus pyogenes citreus.....	27	27	25	26	26
Staphylococcus pyogenes albus .....	27	27	32	31	30
Staphylococcus epidermis albus.....	27	32	28	27	28.5
Bacillus typhosus .....	25	23	25	25	24.5
Bacillus coli communis .....	28	26	24	27	26.25
Bacillus icteroides .....	26	25	23	24	24.5
Bacillus acidi lactici .....	27	25	25	25	25.5
Bacillus enteritidis .....	27	24	23	23	24.25
Bacillus dysenteriae .....	27	22	24	23	24
Vibrio cholerae .....	21	21	21	24	21.75
Bacillus diphtheriae .....	25	22	23	23	23.25
Bacillus anthracis .....	31	26	26	31	28.5
Bacillus pestis .....	23	21	21	22	21.75
Bacillus glanders.....	23	23	24	24	23.5
Bacillus pyocyaneus .....	25	22	21	25	23.25
Bacillus subtilis .....	26	24	21	27	24.5
Bacillus proteus vulgaris .....	27	22	22	21	23
Bacillus megaterium .....	20	20	15	20	18.75
Bacillus prodigiosis .....	20	21	20	20	20.25
Bacillus flourescens liquefaciens .....	23	21	21	20	21.25
Averages .....	25.3	24.1	23.7	24.6	24.4

It was seen from a study of the results obtained that the antiseptic power of glycerin varies with the organism and also with the kind of glycerin used. For example, the growth of cholera and plague is retarded by the presence of 21 to 24 per cent of glycerin, while pus cocci will grow in 31 per cent. The antiseptic power of glycerin "X" and "S" is greater than that of "P" or "G."

It was also seen that the molds and common bacteria of putrefaction grow in bouillon containing between 40 and 50 per cent of glycerin, while the pure culture of the bacteria tested do not grow in percentages above 31.

Attention is especially called to the interesting fact brought out by this series of tests that the pus cocci are able to grow and multiply in higher percentages of glycerin than any of the other 18 micro-organisms tested.

#### THE GERMICIDAL POWER OF GLYCERIN.

The following tests were made to determine the time required for glycerin to destroy the important pathogenic organisms. The work included tests with various percentages of glycerin at different temperatures. Our object was to determine the exact effect of glycerin free from all other substances upon pure cultures. Therefore the bacteria were grown upon agar slants and carefully taken from the surface, so as to obtain the colonies free from the organic matter on which they rested.

#### STAPHYLOCOCCUS PYOGENES AUREUS.

The various percentages of glycerin were made with sterile distilled water and distributed into test tubes. Each tube was abundantly inoculated with a young cul-



ture of *Staphylococcus pyogenes aureus* taken from the surface of an agar slant free of foreign organic matter.

For comparison the organism was also inoculated into sterile distilled water and upon sterile slips of filter paper.

Three sets of tubes were made and kept at different temperatures, as indicated on the table.

From time to time a small quantity (about 0.5 c. c.) of the test fluids and also one of the slips of filter paper was planted in bouillon.

[+ means growth; - means no growth.]

Kept in—	Filter paper.	Dis-tilled water.	Per cent glycerin.																		
			10	20	30	40	50	60	70	80	90	100									
Incubator, 37° C.:																					
7 days.....	+	+	-	-	+	-	-	+	-	-	+	-	-	+	-	-	-	+	-	-	-
13 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
55 days.....	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Room, 22° to 24° C.:																					
7 days.....	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-
13 days.....	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20 days.....	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27 days.....	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34 days.....	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41 days.....	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ice chest, 10° to 12° C.:																					
7 days.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
13 days.....	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
20 days.....	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-
27 days.....	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34 days.....	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41 days.....	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48 days.....	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
55 days.....	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
62 days.....	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
69 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
76 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
83 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
90 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
97 days.....	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
111 days.....	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

#### STAPHYLOCOCCUS EPIDERMIS ALBUS.

The various percentages of glycerin were made with sterile distilled water and distributed into test tubes. Each tube was abundantly inoculated with a young culture of *Staphylococcus epidermis albus*, taken from the surface of an agar slant, free of foreign organic matter.

For comparison the organism was also inoculated into sterile distilled water and upon sterile slips of filter paper.

Three sets of tubes were made and kept at different temperatures, as indicated on the table.

From time to time a small quantity (about 0.5 c. c.) of the test fluids and also one of the slips of filter paper were planted in bouillon.



[+ means growth; - means no growth.]

Kept in—	Filter paper.	Dis-tilled water.	Per cent glycerin.									
			10	20	30	40	50	60	70	80	90	100
Room, 22° to 24° C.—Continued.												
63 days.....		+										
70 days.....		+										
77 days.....		+										
84 days.....		+										
91 days.....		+										
98 days.....		+										
112 days.....		+										
133 days.....		-										
Ice chest, 10° to 12° C.:												
7 days.....	+	+	+	+	+	+	+	+	+	+	+	+
14 days.....	+	+	+	+	+	+	+	+	+	+	+	+
19 days.....	+	+	+	+	+	+	+	+	+	+	+	+
29 days.....	+	+	+	+	+	+	+	+	+	+	-	-
35 days.....	+	+	+	+	+	+	+	+	+	+		
42 days.....	+	+	+	+	-	-	-	-	-	+		
49 days.....	-	+	+	-						+		
56 days.....		+	+									
63 days.....		+	+						(a)			
70 days.....		+	+						+			
77 days.....		+	+						-			
84 days.....		+	+									
91 days.....		+	+									
98 days.....		+	+									
112 days.....		+	-									
133 days.....		+										
154 days.....			(b)									

a Slow.

b Material exhausted.

## DIPHThERIA.

The various percentages of glycerin were made with sterile distilled water and distributed into test tubes. Each tube was abundantly inoculated with a young culture of *diphtheria*, taken from the surface of an agar slant, free of foreign organic matter.

For comparison, the organism was also inoculated into sterile distilled water and upon sterile slips of filter paper.

Three sets of tubes were made and kept at different temperatures, as indicated on the table.

From time to time a small quantity (about 0.5 c. c.) of the test fluids and also one of the slips of filter paper were planted in bouillon.

[+ means growth; - means no growth.]

Kept in—	Filter paper.	Dis-tilled water.	Per cent glycerin.									
			10	20	30	40	50	60	70	80	90	100
Incubator, 37° C.:												
7 days.....	-	+	-	-	-	-	-	-	-	-	-	-
14 days.....		-										
19 days.....												
Room, 22° to 24° C.:												
7 days.....	-	+	-	+	-	-	-	-	-	-	-	-
14 days.....		+		-								
19 days.....		+										
29 days.....		-										
Ice chest, 10° to 20° C.:												
7 days.....	-	+	+	-	-	-	-	-	-	-	-	-
14 days.....	-	+	-									
19 days.....		-										

It will be seen from these experiments that the pathogenic bacteria usually die within a week or ten days in glycerin when exposed at 37° C. in the incubator. At room temperature (22° C.) glycerin is

not so active, the organisms sometimes surviving two weeks. In the ice chest at 10° to 12° C. the germicidal power of glycerin is markedly diminished. Pus cocci live for several weeks, the colon bacillus several months.

It will be noted from these tables that 50 per cent glycerin seems to be more actively germicidal than either stronger or weaker solutions.

The next experiment was made to test the effect of glycerin upon spores, with the following results:

#### BACILLUS ANTHRACIS.

The various percentages of glycerin were made with sterile distilled water and distributed into test tubes. Each tube was abundantly inoculated with a growth of *B. anthracis* containing many spores taken from the surface of peptoneless agar, care being taken to carry over only a culture free from the organic matter of the media used.

For comparison the organism was also inoculated into sterile distilled water and upon sterile slips of filter paper.

Three sets of tubes were made and kept at different temperatures, as indicated on the table.

From time to time a small quantity (about 0.5 c. c.) of the test fluids, and also one of the slips of filter paper, were planted in bouillon. In addition to testing the vegetability of the organism in this manner its virulence was tested from time to time as indicated on the tables by inoculation into mice.



[+ means growth; - means no growth.]

Kept in—	Filter paper.	Distilled water.	Per cent glycerin.										Remarks.			
			10	20	30	40	50	60	70	80	90	100				
Incubator, 37° C.:																
7 days .....	+	+	a+	+	+	+	+	+	+	+	+	+	+	+		
14 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
61 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
97 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
122 days .....	+	+	+	+	+	b-	+	+	+	+	+	+	+	+		
133 days .....	+	+	+	+	+	e+	+	+	+	+	+	+	+	+		
184 days .....	+	+	+	+	+	h+	+	+	+	+	+	+	+	+		
215 days .....	+	-	-	-	-	-	+	+	-	-	k+	-	-			
236 days .....	+	-	-	-	-	-	n+	-	-	-	-	-	-			
247 days .....	-	-	-	-	-	-	-	-	-	-	-	-	-			
Room, 22° to 24° C.:																
7 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+			
14 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+			
61 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+			
97 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+			
122 days .....	+	+	+	+	+	+	+	c+	+	+	+	+	+			
153 days .....	+	+	+	+	+	+	+	f+	+	+	+	+	+			
184 days .....	+	+	+	+	+	+	+	i+	+	+	+	+	+			- slow and scanty growth.
215 days .....	+	+	-	-	-	-	-	-	-	-	l+	+	+			
236 days .....	+	+	-	-	-	-	-	-	-	-	o+	-	-			
247 days .....	-	-	-	-	-	-	-	-	-	-	-	-	-			
Ice chest, 10° to 12° C.:																
7 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+			
12 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+			
61 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+			
97 days .....	+	+	+	+	+	+	+	+	+	+	+	+	+			
122 days .....	+	+	+	+	+	+	+	+	d+	+	+	+	+			
153 days .....	+	+	+	+	+	+	g+	+	+	+	+	+	+			
184 days .....	+	+	+	+	+	+	j+	+	+	+	+	+	+			- slow and scanty growth.
215 days .....	+	+	+	+	-	+	m+	-	+	-	+	+	+			
236 days .....	+	+	p+	+	-	+	-	-	+	-	+	+	+			
247 days .....	+	+	q+	+	+	+	+	-	+	-	+	+	+			
278 days .....	-	+	r+	-	-	+	-	-	-	-	-	-	-			Material exhausted.

(a) No growth first time; growth when replanted.

(b) 0.5 c. c. of the bouillon growth obtained from the 50 per cent glycerin kept in the incubator was inoculated subcutaneously in a mouse; dead in six days.

(c) 0.5 c. c. of the broth growth obtained from the 60 per cent glycerin kept at room temperature was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(d) 0.5 c. c. of the broth growth obtained from the 70 per cent glycerin kept in the ice chest was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(e) 1 c. c. of the bouillon growth obtained from the 50 per cent glycerin kept in the incubator was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(f) 1 c. c. of the bouillon growth obtained from the 60 per cent glycerin kept at room temperature was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(g) 1 c. c. of the bouillon growth obtained from the 50 per cent glycerin kept in the ice chest was inoculated subcutaneously in a mouse; dead in twenty-four hours.

(h) 1 c. c. of the bouillon growth obtained from the 50 per cent glycerin kept in the incubator was inoculated subcutaneously in a mouse; dead in seventy-two hours.

(i) 1 c. c. of the bouillon growth obtained from the 60 per cent glycerine kept at room temperature was inoculated subcutaneously in a mouse; dead in seventy-two hours.

(j) 1 c. c. of the bouillon growth obtained from the 50 per cent glycerin kept in the ice chest was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(k) 1 c. c. of the bouillon growth obtained from the 90 per cent glycerin kept in the incubator was inoculated subcutaneously in a mouse; dead in eighty-four hours.

(l) 1 c. c. of the bouillon growth obtained from the 90 per cent glycerin kept at room temperature was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(m) 1 c. c. of the bouillon growth obtained from the 50 per cent glycerin kept in the ice chest was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(n) 1 c. c. of the bouillon growth obtained from the 60 per cent glycerin kept in the incubator was inoculated subcutaneously in a mouse; dead in sixty hours.

(o) 1 c. c. of the bouillon growth obtained from the 90 per cent glycerin kept at room temperature was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(p) 1 c. c. of the bouillon growth obtained from the 10 per cent glycerin kept in the ice chest was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(q) 1 c. c. of the bouillon growth obtained from the 10 per cent glycerin kept in the ice chest was inoculated subcutaneously in a mouse; dead in forty-eight hours.

(r) 1 c. c. of the bouillon growth obtained from the 10 per cent glycerin kept in the ice chest was inoculated subcutaneously in a mouse; dead in forty-eight hours.



It will be seen from this table that glycerin has practically no effect upon spores. They remain alive and virulent over two hundred days in all percentages of glycerin at temperatures of 37°, 22°, and 10° C.

The following series of tests were made to estimate more precisely the germicidal power of glycerin by counting the colonies from day to day and determining the rate of diminution.

It will be seen from these studies that glycerin produces its greatest germicidal effect during the first twenty-four hours. The more resisting members of the colonies which survive this first period are able to resist the action of the glycerin much longer when they also finally succumb.

## STAPHYLOCOCCUS PYOGENES AUREUS.

The various percentages of glycerin (P.) mixed with distilled water were inoculated with a young culture of *B. staphylococcus pyogenes aureus* free of foreign organic matter and then each flask containing the test fluid was thoroughly shaken so as to make as uniform an emulsion as possible. The shaking was repeated each time before the fluid was withdrawn for the purpose of making the counts.

One series of flasks was kept in the ice chest at 10° to 12° C. and another in the incubator at 37° C.

The figures represent the number of organisms (i. e., colonies) per cubic centimeter.

When counted.	Distilled water.		20 per cent glycerin.		50 per cent glycerin.		80 per cent glycerin.		Pure glycerin.	
	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.
At once ..	4,420,000	1,290,000	464,000	253,000	64,000	66,000	4,200,000	3,376,000	+	+
1 day ...	104,000	1,050,000	3,000	12,000	1,000	22,000	+	840,000	+	+
2 days ...	120,000	408,000	—	+	1,000	12,000	+	66,000	—	+
3 days ...	3,000	920,000	.....	—	—	2,000	+	12,000	.....	+
4 days ...	—	110,000	.....	.....	.....	2,500	75	+	.....	—
5 days ...	.....	88,000	.....	.....	.....	25	—	—	.....	.....
6 days ...	.....	60,000	.....	.....	.....	—	.....	.....	.....	.....
8 days ...	.....	70,000	.....	.....	.....	.....	.....	.....	.....	.....
12 days ...	.....	89,000	.....	.....	.....	.....	.....	.....	.....	.....
17 days ...	.....	19,000	.....	.....	.....	.....	.....	.....	.....	.....
22 days ...	.....	28,000	.....	.....	.....	.....	.....	.....	.....	.....
27 days ...	.....	22,000	.....	.....	.....	.....	.....	.....	.....	.....
31 days ...	.....	15,000	.....	.....	.....	.....	.....	.....	.....	.....

When counted.	Distilled water.		50 per cent glycerin.		Pure glycerin.	
	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.
At once .....	4,060	3,900	10,400,000	15,750,000	1,395,000	3,530,000
1 day .....	185	140	110	1,575,000	100	1,200,000
2 days .....	1	0	0	630,000	25	25,200
3 days .....	1	{ Bouillon + Agar -0	0	126,000	0	Bouillon + Agar -0
4 days .....	{ -Bouillon -Agar 0	-Bouillon -0	-Bouillon 0	37,800	-Bouillon 0	+Bouillon 1 +Agar (1)
5 days .....	-In bouillon 0	-In bouillon 0	-In bouillon 0	15,900	-In bouillon 0	-In bouillon 0
6 days .....	0	0	0	1,980	0	0
7 days .....	.....	.....	.....	542	.....	.....
8 days .....	.....	.....	.....	150	.....	.....
9 days .....	.....	.....	.....	83	.....	.....
10 days <sup>a</sup> .....	.....	.....	.....	1	.....	.....
12 days .....	.....	.....	.....	0	.....	.....
13 days .....	.....	.....	.....	.....	.....	.....

<sup>a</sup>Left in room.

## BACILLUS TYPHOSUS.

The various percentages of glycerin (S.) mixed with distilled water were inoculated with a young culture of *B. typhosus* free of foreign organic matter, and then each flask containing the test fluid was thoroughly shaken so as to make as uniform an emulsion as possible. The shaking was repeated each time before the fluid was withdrawn for the purpose of making the counts.

One series of flasks was kept in the ice chest at 10° to 12° C. and another in the incubator at 37° C.

The figures represent the number of organisms (i. e., colonies) per cubic centimeter.

When counted.	Distilled water.		20 per cent glycerin.		50 per cent glycerin.		80 per cent glycerin.		Pure glycerin.	
	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.
At once	10,710,000	11,655,000	180,000	118,000	115,000	124,000	2,000	3,000	2,000	2,000
1 day	5,040,000	21,630,000	150,000	26,000	86,000	4,000	1,000	1,000	+	+
2 days	380,000	9,450,000	—	500	1,000	1,000	2	+	—	—
3 days	70,000	10,710,000	—	300	10	26	—	—	—	—
4 days	11,000	10,290,000	—	80	28	3	—	—	—	—
5 days	29	8,400,000	—	56	—	—	—	—	—	—
6 days	—	4,480,000	—	—	—	—	—	—	—	—
7 days	—	4,410,000	—	—	—	—	—	—	—	—
10 days	—	4,000,000	—	—	—	—	—	—	—	—
13 days	—	3,860,000	—	—	—	—	—	—	—	—
16 days	—	4,100,000	—	—	—	—	—	—	—	—
21 days	—	5,080,000	—	—	—	—	—	—	—	—
26 days	—	452,000	—	—	—	—	—	—	—	—
31 days	—	600,000	—	—	—	—	—	—	—	—

## BACILLUS COLI COMMUNIS.

The various percentages of glycerin (M. & R.) mixed with distilled water were inoculated with a young culture of *B. coli communis* free of foreign organic matter, and then each flask containing the test fluid was thoroughly shaken so as to make as uniform an emulsion as possible. The shaking was repeated each time before the fluid was withdrawn for the purpose of making the counts.

One series of flasks was kept in the ice chest at 10° to 12° C. and another in the incubator at 37° C.

The figures represent the number of organisms (i. e., colonies) per cubic centimeter.

When counted.	Distilled water.		20 per cent glycerin.		50 per cent glycerin.		80 per cent glycerin.	
	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.
At once	3,760,000	8,064,000	4,440,000	4,680,000	2,416,000	1,760,000	500,000	664,000
1 day	9,660,000	11,708,000	19,000	131,000	+	28,000	+	181,000
2 days	7,728,000	6,410,000	3,000	56,000	+	630,000	+	14,000
3 days	6,930,000	8,190,000	84	4,200	129	28,000	420	17,010
4 days	5,670,000	9,450,000	4	42,000	—	3,000	+	111,000
5 days	6,130,000	9,210,000	2	51,000	—	12,600	100	1,000
6 days	7,630,000	7,630,000	—	10,000	—	+	2	+
7 days	4,330,000	8,400,000	—	2,000	—	1	—	+
8 days	4,250,000	9,800,000	—	2,700	—	—	—	—
9 days	3,465,000	7,770,000	—	1,000	—	—	—	—
10 days	3,523,000	7,805,000	—	100	—	—	—	—
12 days	2,870,000	8,440,000	—	100	—	—	—	—
14 days	1,600,000	6,440,000	—	40	—	—	—	—
16 days	880,000	1,290,000	—	9	—	—	—	—
17 days	515,000	6,300,000	—	4	—	—	—	—
19 days	480,000	5,230,000	—	8	—	—	—	—
21 days	390,000	8,400,000	—	—	—	—	—	—
23 days	340,000	4,410,000	—	—	—	—	—	—
24 days	370,000	4,000,000	—	—	—	—	—	—
26 days	280,000	5,200,000	—	—	—	—	—	—
29 days	102,000	7,500,000	—	—	—	—	—	—
31 days	104,000	10,080,000	—	—	—	—	—	—

## BACILLUS COLI COMMUNIS.

The various percentages of glycerin (P.) mixed with distilled water were inoculated with a young culture of *B. coli communis* free of foreign organic matter, and then each flask containing the test fluid was thoroughly shaken so as to make as uniform an emulsion as possible. The shaking was repeated each time before the fluid was withdrawn for the purpose of making the counts.

One series of flasks was kept in the ice chest at 10° to 12° C. and another in the incubator at 37° C.

The figures represent the number of organisms (i. e., colonies) per cubic centimeter.

When counted.	Distilled water.		20 per cent glycerin.		50 per cent glycerin.		80 per cent glycerin.		Pure glycerin.	
	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.
At once ..	4, 410, 000	20, 700, 000	3, 632, 000	11, 900, 000	210, 000	1, 582, 000	408, 000	400, 000	10, 000	2, 000
1 day ..	4, 427, 000	1, 610, 000	3, 000	5, 040, 000	+	+	4, 000	1, 000	1, 000	+
2 days ..	4, 200, 000	7, 560, 000	1	4, 550, 000	11	500, 000	—	8, 000	—	93, 000
3 days ..	18, 900, 000	9, 520, 000	—	4, 410, 000	—	15, 000	—	—	—	—
4 days ..	8, 922, 000	7, 376, 000	—	2, 800, 000	—	29, 200	—	—	—	—
5 days ..	8, 443, 000	8, 400, 000	—	110, 000	—	16, 000	—	—	—	—
6 days ..	7, 700, 000	8, 470, 000	—	8, 000	—	22, 000	—	—	—	—
7 days ..	3, 500, 000	9, 500, 000	—	1, 000	—	3, 000	—	—	—	—
8 days ..	Flask broken.	11, 000, 000	—	600	—	900	—	—	—	—
9 days ..	—	12, 000, 000	—	18	—	200	—	—	—	—
11 days ..	—	14, 000, 000	—	24	—	4	—	—	—	—
13 days ..	—	17, 000, 000	—	15	—	—	—	—	—	—
15 days ..	—	14, 280, 000	—	5	—	—	—	—	—	—
16 days ..	—	10, 710, 000	—	2	—	—	—	—	—	—
18 days ..	—	13, 860, 000	—	—	—	—	—	—	—	—
20 days ..	—	10, 290, 000	—	—	—	—	—	—	—	—
24 days ..	—	11, 600, 000	—	—	—	—	—	—	—	—
27 days ..	—	9, 480, 000	—	—	—	—	—	—	—	—
31 days ..	—	8, 640, 000	—	—	—	—	—	—	—	—

## BACILLUS DIPHTHERIÆ.

The various percentages of glycerin (P.) mixed with distilled water were inoculated with a young culture of *B. diphtheriæ* free of foreign organic matter, and then each flask containing the test fluid was shaken so as to make as uniform an emulsion as possible. The shaking was repeated each time before the fluid was withdrawn for the purpose of making the counts.

One series of flasks was kept in the ice chest at 10° to 12° C. and another in the incubator at 37° C.

The figures represent the number of organisms (i. e., colonies) per cubic centimeter.

When counted.	Distilled water.		50 per cent glycerin.		100 per cent glycerin.		Remarks.
	Incubator.	Ice chest.	Incubator.	Ice chest.	Incubator.	Ice chest.	
At once ..	1, 080	2, 450	10	—	20	10	All sterile in bouillon.
1 day ..	0	0	1	0	0	1	
2 days ..	0	0	0	0	0	0	

It is again evident from these experiments that the pus cocci in pure culture are destroyed by the action of glycerin within two weeks.

Glycerin seems to be an active poison for the bacillus of diphtheria throughout all our experiments.

The organisms belonging to the typhoid and colon group sometimes show a more marked resistance in some of our other tests than the preceding.











Pus from a bone felon of the finger, containing *Staphylococcus pyogenes albus* in pure culture, planted in various percentages of glycerin (G) in distilled water and kept in the incubator at 37° C. From time to time small portions of the emulsion were drawn off and planted upon agar and in bouillon.

Days.	Percentage of glycerin.										Remarks.
	10	20	30	40	50	60	70	80	90	100	
7.....	+	+	+	-	-	-	-	-	-	-	All marked — gave no growth in broth.
14.....	+	+	+	.....	.....	.....	.....	.....	.....	.....	
21.....	+	+	+	.....	.....	.....	.....	.....	.....	.....	
28.....	+	+	+	.....	.....	.....	.....	.....	.....	.....	
35.....	+	-	-	.....	.....	.....	.....	.....	.....	.....	
42.....	-	-	-	.....	.....	.....	.....	.....	.....	.....	

#### STAPHYLOCOCCUS IN PURE CULTURE FROM ABOVE PUS.

A pure culture of *Staphylococcus pyogenes albus* isolated from the above pus obtained from a bone felon of the finger was planted in various percentages of glycerin and tested as above.

Days.	Percentage of glycerin.										Remarks.
	10	20	30	40	50	60	70	80	90	100	
7.....	+	+	+	-	-	-	-	-	-	-	All marked — gave no growth in broth.
14.....	+	+	+	-	-	-	-	-	-	-	
21.....	+	+	+	-	-	-	-	-	-	-	
28.....	+	+	+	.....	.....	.....	.....	.....	.....	.....	
35.....	+	+	+	.....	.....	.....	.....	.....	.....	.....	
42.....	+	-	+	.....	.....	.....	.....	.....	.....	.....	
49.....	+	-	+	.....	.....	.....	.....	.....	.....	.....	
56.....	-	-	-	.....	.....	.....	.....	.....	.....	.....	

From these experiments it will be seen that glycerin has the power of destroying pus organisms whether in pure culture or in the pus itself within two weeks when exposed at these temperatures. As these tests were made in the incubator at 37° C. they can not be taken as an evidence of what glycerin may always do in vaccine virus when kept cool.

#### TETANUS IN GLYCERIN.

##### VIABILITY OF TETANUS IN GLYCERIN.

On January 2, 1903, tetanus was planted into 1,000 c. c. of ordinary bouillon and grown two weeks in a Novy jar at 37° C. Examination of the growth showed that it was a pure culture. The spores and toxin were then separated by filtration and the toxin was set aside.

The spores were diluted with distilled water and filtered. The residue was again suspended in water and filtered several times in order to remove the toxin. 1,000 c. c. were used in the washing.







The spores kept in various percentages of glycerin in the incubator have apparently died out, viz, having failed to produce symptoms when inoculated directly into mice. Tests were now made (May 9) to see whether these spores were really dead or whether their virulence was simply attenuated. Small quantities from each of the test dilutions were therefore inoculated into freshly prepared bouillon and grown anærobically in a Novy jar in an atmosphere of hydrogen plus pyrogallic acid and caustic potash, with the following results:

*Planted May 9.*

Mixture.	Result.
Aqueous solution.....	Growth, no spores, contaminated.
10 per cent glycerin.....	Mixed, no spores, contaminated.
20 per cent glycerin.....	No growth.
30 per cent glycerin.....	Many spores.
40 per cent glycerin.....	Many spores and rods.
50 per cent glycerin.....	Many spores and rods.
60 per cent glycerin.....	Many spores.
70 per cent glycerin.....	Many spores.
80 per cent glycerin.....	Many spores.
90 per cent glycerin.....	Spores and many rods.
100 per cent glycerin.....	Many spores.

A few drops of the growths thus obtained were on May 21 inoculated into mice, with the result that all died within a few hours without showing characteristic symptoms. The inoculations were repeated June 3 (i. e., 25 days' growth in bouillon), 0.0005 c. c. was inoculated subcutaneously into the flank of each mouse, with the following results:

[+ = typical symptoms of tetanus; - = no symptoms of tetanus; k = killed; d = died.]

Quantity inoculated into mice, percentage of glycerin, and temperature.	Result.											
	1st day.	2d day.	3d day.	4th day.	5th day.	6th day.	7th day.	8th day.	9th day.	10th day.	11th day.	12th day.
Incubator:												
0.0005 c. c. distilled water.....	+k	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
10 per cent glycerin.....	+k	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
20 per cent glycerin.....	-a	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
30 per cent glycerin.....	+k	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
40 per cent glycerin.....	+k	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
50 per cent glycerin.....	+k	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
60 per cent glycerin.....	+k	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
70 per cent glycerin.....	+k	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
80 per cent glycerin.....	+d	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
90 per cent glycerin.....	+d	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
100 per cent glycerin.....	+d	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....

a. This showed no growth. Therefore about 0.25 c. c. of the dilution was injected into a mouse. No symptoms.

The dilutions, etc., for the others were as follows: 10 c. c. aq. + 0.1 c. c. spores = 1:100. 0.05 c. c. of this solution would contain 1/2000 of the original, or .0005.

Showing that although the spores had lost their power of producing tetanus when inoculated directly into mice, they were not dead, as they regained their original activity and virulence when reactivated by growing under favorable conditions.



*Tetanus spores.*

## AFTER ONE HUNDRED AND TWENTY DAYS' EXPOSURE TO GLYCERIN.

[+ = typical symptoms of tetanus; - = no symptoms of tetanus; k = killed; d = died.]

Quantity inoculated into mice, percentage of glycerin, and temperature.	Result.											
	1st day.	2d day.	3d day.	4th day.	5th day.	6th day.	7th day.	8th day.	9th day.	10th day.	11th day.	12th day.
Incubator, 37° C.:												
0.05 c. c. distilled water.....												
20 per cent glycerin.....												
40 per cent glycerin.....												
60 per cent glycerin.....												
80 per cent glycerin.....												
100 per cent glycerin.....												
Ice chest, 10° to 12° C.:												
0.05 c. c. distilled water.....												
20 per cent glycerin.....	-	+	+k									
40 per cent glycerin.....	-	+	+k									
60 per cent glycerin.....	-	?	+	+	+	+k						
80 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
100 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
Room, about 20° C.:												
0.05 c. c. distilled water.....	-	-?	-	-	-	-	-	-	-	-	-	-
20 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
40 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
60 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
80 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
100 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-

## AFTER ONE HUNDRED AND FIFTY DAYS' EXPOSURE TO GLYCERIN.

Ice chest, 10° to 12° C.:												
0.05 c. c. 10 per cent glycerin.....	-	+	+	+k								
30 per cent glycerin.....	-	+k										
50 per cent glycerin.....	-	+k										
70 per cent glycerin.....	-	-	+	+	+	+k						
90 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
Room, about 20° C.:												
0.05 c. c. 10 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
30 per cent glycerin.....	-	-	+	+	+	+k						
50 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
70 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
90 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-

## AFTER ONE HUNDRED AND EIGHTY DAYS' EXPOSURE TO GLYCERIN.

Ice chest, 10° to 12° C.:												
0.05 c. c. 20 per cent glycerin.....	-	?	+k									
40 per cent glycerin.....	-	+k										
60 per cent glycerin.....	-	+	+k									
80 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
100 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
Room, about 20° C.:												
0.05 c. c. 20 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
40 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
60 per cent glycerin.....	-	-	?	+k								
80 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-
100 per cent glycerin.....	-	-	-	-	-	-	-	-	-	-	-	-

We learn from these studies that tetanus spores may die within thirty days in glycerin at the body temperature; but they live for months (one hundred and eighty days) at room temperature or in the ice chest. The virulence of the spores is generally lost long before their power of growing and multiplying if placed under favorable conditions.

## TETANUS TOXIN IN GLYCERIN.

A series of tests was then made to determine the effect of glycerin upon tetanus toxin.

In each instance a quantity of the glycerin containing 0.0025 c. c. of the toxin was inoculated into the flank of a mouse and observed for symptoms. This quantity was over ten times the M. L. D.

It was found that the toxin exposed to the glycerin gradually lost its virulence after sixty days at the body temperature, but that it was still active after one hundred and eighty days in the ice chest or at room temperature.

If vaccine virus, therefore, was contaminated with such toxin the glycerin would have no influence upon it.

VIABILITY OF MIXED CULTURE OF TETANUS IN VARIOUS PERCENTAGES OF GLYCERIN.

This culture was the same as was used for testing the viability of the mixed culture of tetanus on dry points and in glycerinated virus.<sup>a</sup> It was planted into 400 c. c. of bouillon on June 25 and kept at 37° for two weeks in a Novy jar. It contained a coccus, a slender motile rod of good length, which contained a central oval spore, in addition to a rich growth of tetanus organisms.

On July 14 the 400 c. c. were subjected to a Pasteur filter to remove the toxins. The residue was washed several times with distilled water to remove any trace of toxins from the tetanus organisms. The excess of water in which the tetanus remained suspended was evaporated in a vacuum containing a vessel of calcium chloride until it reached a bulk of about 2 c. c.

Three series of test tubes were prepared. Each series represented ten different percentages of pure glycerin in water, namely, 10, 20, 30 per cent, etc., to 100 per cent. Into each of the thirty tubes comprising the three series we put an equal amount of the watery suspension of mixed tetanus organisms on July 16 and paraffined the cotton plugs. The three series were then put at different temperatures—one at room temperature, about 20° C.; another in the incubator at 37°, and the other in the ice chest at 10° to 12° C. Before placing the series at different temperatures, however, they were tested on mice.

As a control, inoculations into mice were made from three tubes selected at random, which were the 10 per cent incubator, 30 per cent ice chest, and 60 per cent room temperature. The three series were then placed in their appropriate temperatures and tested on mice at intervals.

It was found that mixed cultures of tetanus in glycerin at the body

<sup>a</sup>See Bulletin No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.

heat began to lose their virulence in thirty days, but at room temperature were virulent for mice at the end of ninety days, and in the ice chest at one hundred and sixty-five, when all of the material was exhausted.

#### RÉSUMÉ AND CONCLUSIONS.

This study was undertaken and is published on account of its importance from a public-health standpoint, particularly in view of the fact that glycerin is used to conserve vaccine virus and analogous products. On account of its bland and nonpoisonous properties glycerin has long been used as a preservative for organic matter; but not until 1891, when Copeman claimed for it special virtues as a germicide, did it come into general use to purify vaccine virus.

A false sense of security arose owing to an overestimate of the antiseptic and germicidal value of glycerin. This fact we have brought out in previous publications on the subject of the bacteriological impurities of vaccine virus. Other substances, such as chloroform vapor, chloretone, potassium cyanide, carbolic acid, formalin, etc., have since been used as a substitute for glycerin with more or less success, and it is possible that one of these more energetic germicidal substances may be found to be superior to glycerin for this particular purpose in commercial practice.

The experiments are published in detail at the request of several vaccine producers who desire to know the exact value of glycerin as a germicide and antiseptic.

In brief, it may be stated that glycerin has distinct but very feeble germicidal and antiseptic properties. The results are summarized as follows:

#### GLYCERIN AS AN ANTISEPTIC.

Small quantities of glycerin, less than 10 per cent, added to nutrient media have well-known powers of favoring the growth and multiplication of many forms of bacteria.

The presence of 50 per cent of glycerin will restrain all bacterial growth. Less than this amount can not be depended upon for the preservation of vaccines and other organic growths.<sup>a</sup>

The antiseptic power varies for the different glycerins. For instance, some restrain all growth and development when present in the proportion of 43 per cent; others require 49 per cent.

No evident growth or multiplication of bacteria takes place in nutrient media containing 32 per cent of glycerin, but molds grow in stronger percentages, viz, 40 to 49 per cent.

In order to prevent the growth and development of pus cocci at least 33 per cent of glycerin must be present. This is more than that

<sup>a</sup> The percentages throughout this paper are by volumes.

required to restrain the growth and multiplication of the other eighteen different pathogenic and saprophytic bacteria tested.

#### GLYCERIN AS A GERMICIDE.

Glycerin has a distinct, though exceedingly feeble, germicidal action. It probably acts by virtue of its great affinity for water, abstracting this substance from the germ.

As a rule, glycerin destroys the micrococci of suppuration, whether these be in pure culture or in the pus itself, within two weeks. This action, like that of all germicides, depends for its activity upon the temperature. Pus cocci may live in glycerin for months in the ice chest. They would die in a week at the body temperature.

Glycerin seems to be a selective poison for the bacillus of diphtheria, which in all of our experiments died much more quickly than any of the other organisms tested.

The bacteria of the typhoid and colon group often show a marked resistance to the effects of glycerin in strong proportions.

Glycerin asserts its greatest germicidal effect during the first twenty-four hours. The remaining members of the colonies which resist its action for this first period succumb very slowly.

Glycerin in all proportions has practically no effect upon endogenous spores. We have kept anthrax spores alive and virulent two hundred days in the stronger percentages and at warm temperatures.

#### TETANUS IN GLYCERIN.

Tetanus spores in pure culture, freed of all organic matter and washed free of toxin, may lose their virulence in glycerin in thirty days at the body temperature, but they live for months (one hundred and eighty days) at room temperature or in the ice chest. Glycerin, therefore, can not be depended upon to purify vaccine or other organic matter containing this contamination. The virulence of the spores is lost long before they actually die, for they still retain the power of growing and multiplying if placed under favorable conditions. Under these circumstances they also regain their original pathogenic properties.

Glycerin has practically no effect upon tetanus toxin. We found such toxin added to glycerin to be active for sixty days at the body temperature and one hundred and eighty days at room temperature or in the ice chest.







TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 17.

M. J. ROSENAU, Director.

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# ILLUSTRATED KEY

TO THE

# TREMATODE PARASITES OF MAN.

BY

CH. WARDELL STILES.



WASHINGTON:  
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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 17.

M. J. ROSENAU, Director.

August, 1904.

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# ILLUSTRATED KEY

TO THE

# TREMATODE PARASITES OF MAN.

BY

CH. WARDELL STILES.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.

1904.

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# ILLUSTRATED KEY TO THE TREMATODE PARASITES OF MAN.

By CH. WARDELL STILES, Ph. D., Chief of Division of Zoology, Hygienic Laboratory,  
United States Public Health and Marine-Hospital Service.

## INTRODUCTION.

Upon several recent occasions the writer has been called upon for information in regard to the trematodes which are parasitic in man, and it is in response to such requests that the present paper is published. This key is offered not as an exhaustive treatment of the subject, but as a ready reference aid in clinical diagnosis.

To the American physician the trematodes or flukes have been heretofore chiefly matters of scientific interest, most men looking upon them as zoological curiosities. Hepatic distomatosis, caused by *Fasciola hepatica* and *F. magna*, is known to occur in cattle, particularly in the Southern States; *F. hepatica* is also found in sheep in various parts of the country, and it need not be surprising if isolated cases of infection with this parasite should be found in man. About 20 cases of hepatic distomatosis, caused by *Opisthorchis sinensis*, have already been found in this country, and it is strange that the cases thus far seen are so few in number. Parasitic hemoptysis, caused by *Paragonimus westermanii*, has been found in the United States in dogs, cats, and swine, and one (imported) case in man has recently been recognized in Portland, Oreg. Bilharziosis, caused by *Schistosoma hæmatobium*, has been found in this country upon at least three occasions, and it is also said to occur in Cuba and Porto Rico. Thus, for the American physician, trematode diseases are becoming something more than a mere matter of curiosity, and their importance is increased by the fact that about 120,000 of our troops have been serving in the Asiatic quarter of the globe, or, in other words, in a part of the world where maladies of trematode origin are more common than they are with us. Whether the return of these troops, together with the return of travelers from Asia, will result in making these diseases more or less common in man in the United States can not be definitely prophesied, but the indications are that we shall not entirely escape infection. It is difficult to guard against the introduction of the parasites under consideration, and the question whether they will multiply here depends primarily upon two factors, namely, first,



whether there exist in the United States species of snails which can serve as intermediate hosts; and, second, whether these snails actually become infected by persons harboring the parasites. From the fact that snails are necessary for the propagation of at least some of the trematode maladies of man, it is apparent that cases of infection are more likely to occur in rural districts than in cities. In other words, they are more likely to occur in the practice of a class of physicians who as a rule do not use the microscope as an aid in diagnosis and who, therefore, will not recognize the exact nature of the malady.

#### CLINICAL CLASSIFICATION OF TREMATODE INFECTIONS (DISTOMATOSIS).

Trematode infection is usually spoken of as *distomatosis*. The name is derived from *Distoma*, which has been used by many authors to designate a collective genus in the family Fasciolidæ. As a generic name, *Distoma* is now suppressed, its species having been distributed in a large number of well-defined genera, but the term *distomatosis* may be conveniently retained (at least until the zoologic nomenclature becomes more settled) to designate infection by digenetic trematodes.

Distomatosis may affect different parts of the human body, as follows:

- Ophthalmic distomatosis*: Very rare: diagnosis only by ophthalmoscopic examination, or after operation, or on autopsy: treatment surgical: caused by *Monostomulum* (p. 12), and *Agamodistomum* (p. 12).
- Cerebral distomatosis* (Jacksonian epilepsy): Usually in connection with pulmonary distomatosis; diagnosis symptomatic and by microscopic examination of sputum: no specific treatment: caused by *Paragonimus* (p. 14).
- Pulmonary distomatosis* (parasitic hemoptysis): Diagnosis by microscopic examination of sputum: no specific treatment: caused by *Paragonimus* (p. 14) and *Fasciola* (p. 18).
- Hepatic distomatosis*: Diagnosis by microscopic examination of feces: no specific treatment: caused by *Fasciola*, *Dicrocoelium*, and *Opisthorchis* (p. 20).
- Pancreatic distomatosis*: Occasionally occurs with hepatic infection: caused by *Opisthorchis* (p. 30).
- Intestinal distomatosis*: Diagnosis by microscopic examination of feces: treatment with thymol, or same anthelmintics as for tapeworms: caused by *Fasciolopsis*, *Heterophyes*, and *Gastrodiscus* (p. 39).
- Venal distomatosis* (bilharzian hematuria): Diagnosis, microscopic examination of urine and feces: treatment, male fern (?): caused by *Schistosoma* (p. 49).

#### CLINICAL DIAGNOSIS.

The clinical diagnosis of distomatosis should be made by microscopic examination of the sputum, urine, and feces. No special technique is required. Examine the fresh unstained excretions under a medium

power and later under a higher power dry lens. It will not always be possible to determine from the microscopic examination alone whether the infection is hepatic or intestinal, as the size of the eggs varies and the exact species can not always be definitely determined from the egg.

KEY TO THE EGGS OF TREMATODES REPORTED FOR MAN.

(For species thus far found in the United States, follow Roman type.)

- |   |  |
|---|--|
| 1. Eggs in sputum; embryo not developed. Parasitic hemoptysis.....  | 2                                      |
| Eggs in feces; embryo developed or undeveloped .....  | 3                                      |
| Eggs in urine; 120 $\mu$ long by 50 $\mu$ broad; provided with a 20 $\mu$ long terminal or subterminal spine; contain no embryo when first oviposited, but embryo may develop before egg is discharged from the host. Bilharziosis (Egyptian hematuria) ..... | <i>Schistosoma haematobium</i> (p. 50) |
| 2. Egg 68 to 118 $\mu$ long by 48 to 60 $\mu$ broad. This is the egg usually found in parasitic hemoptysis .....  | <i>Paragonimus westermanii</i> (p. 16) |
| Egg 150 to 190 $\mu$ long by 75 to 90 $\mu$ broad. Very rare in man .....   | <i>Fasciola gigantica</i> (p. 19)      |

EGGS IN FECES.

- |  |  |
|--|--|
| 3. The same egg also in the sputum .....   | 1                                      |
| The same egg may also be in the urine .....  | 1                                      |
| The same egg neither in the sputum nor in the urine.....   | 4                                      |
| 4. Egg more than 100 $\mu$ long .....  | 5                                      |
| Egg less than 50 $\mu$ long.....   | 6                                      |
| 5. Egg 130 to 145 $\mu$ long by 70 to 90 $\mu$ broad; does not contain embryo when discharged in feces. Indicates infection of the liver. <i>Fasciola hepatica</i> (p. 22) |  |
| Egg 120 to 130 $\mu$ long by 77 $\mu$ broad; does not contain embryo when discharged in the feces. Indicates infection of the intestine.....                               | <i>Fasciolopsis buskii</i> (p. 41)     |
| Egg 150 $\mu$ long by 80 $\mu$ broad. Indicates infection of the intestine.....  | <i>Fasciolopsis rathouisi</i> (p. 42)  |
| Egg 150 $\mu$ long by 72 $\mu$ broad. Indicates infection of the intestine.....  | <i>Gastrodiscus hominis</i> (p. 46)    |
| 6. Egg contains embryo .....   | 7                                      |
| Not stated whether egg contains embryo; egg 34 $\mu$ long by 19 to 21 $\mu$ broad. Indicates infection of the liver .....  | <i>Opisthorchis noverca</i> (p. 33)    |
| 7. Embryo with two dark spots in posterior half; egg dark, 38 to 45 $\mu$ long by 22 to 30 $\mu$ broad. Indicates infection of the liver ....                              | <i>Dicrocoelium lanceatum</i> (p. 29)  |
| Embryo without said spots.....   | 8                                      |
| 8. Egg 26 to 30 $\mu$ long by 11 to 15 $\mu$ broad. Indicates infection of the liver.....  | <i>Opisthorchis felineus</i> (p. 31)   |
| Egg 28 to 30 $\mu$ long by 16 to 17 $\mu$ broad. Indicates infection of the liver ..   | <i>Opisthorchis sinensis</i> (p. 35)   |
| Egg 20 to 30 $\mu$ long by 15 to 17 $\mu$ broad. Indicates infection of the intestine....  | <i>Heterophyes heterophyes</i> (p. 45) |

THE PARASITES OF DISTOMATOSIS.

Except in cases of intestinal distomatosis and occasionally in hepatic infection, the physician will rarely, if ever, see the parasite during the life of his patient. If trematodes are found on autopsy, they may be determined by use of the key given on p. 11.

## ANATOMICAL STRUCTURE OF TREMATODES.

The following technical description shows the systematic position and general structure of the flukes under discussion:

[Suborder Malacocotylea: Digenea. Families Monostomidæ, Fasciolidæ, Paramphistomidæ, and Schistosomidæ. See figs. 13-15, 18, 20, 42-47, 49-50, 64, 67-68, 78, 85-86.]

With the exception of the blood flukes (*Schistosoma*) they are all hermaphrodites. They are flat, cylindrical, or conical worms, always longer than broad; on the anterior extremity is situated the mouth, surrounded by a muscular organ, known as the *oral sucker* and curved slightly ventrad. There is a second sucker (the *acetabulum*), which is situated in the ventro-median line; in the Fasciolidæ the acetabulum is generally found on the anterior half of the body, while in the family Paramphistomidæ it is at or near the posterior extremity. The surface of the worms is generally more or less covered with minute spines or tubercles.

The *digestive tract* consists of the mouth, a short esophagus, and two blind sacs (intestinal ceca), which represent the true intestine. The anterior portion of the esophagus is generally connected with the mouth by a muscular bulb (the *pharynx*); the posterior extremity bifurcates, one branch being connected with each intestinal cecum. The intestinal sacs are usually simple elongated tubes (fig. 43), but in the genus *Fasciola* they branch freely (fig. 20, *i*). In *Schistosoma* the two ceca unite after passing the genital glands. An anus is never present.

*Genital organs.*—The *genital pore* is in the ventro-median line in nearly all species here described, the male copulatory organ (*cirrus*, or penis,) lying very close to the female opening (*vulva*). *Male organs:* A cirrus is frequently seen extruded from the genital pore, and in these cases it appears as a curved organ, varying in size according to the species; usually the cirrus is invaginated into the *cirrus pouch*. Through its center runs a canal (the *ductus ejaculatoris*), which receives the spermatozoa from a *resicula seminalis*. The latter is partially or entirely included in the pouch; at its posterior end it receives either directly or indirectly the two *vasa efferentia*, through which the spermatozoa are conducted from the testicles. The testicles, generally two in number, one right and one left, are more or less round, lobate, or branched. *Female organs:* The vulva leads into a canal, the anterior portion of which is known as the *metratrum*; this is continued as the *uterus*, which forms more or less numerous folds in the median portion of the body, and finally leads to the so-called *shell-gland*, which may frequently be seen in fresh specimens (*Fasciola magna* and others) as a round body a short distance posterior of the acetabulum. In the center of the shell-gland is a canal (the *ootype*), in which four canals (*uterus*, *oviduct*, *Laurer's canal*, and *vitelloduct*) come together. The *ovary* in some species is globular, in others lobate, or branched, and connects with the ootype through the *oviduct*. The *Laurer's canal* runs from the ootype dorsad, and opens to the exterior on the dorsal surface. Its function is still doubtful, but homologically it represents the uterus of cestodes. The *vitellogene glands* (vitellaria) are two in number, and are situated laterally of the longitudinal intestinal ceca; they vary in size in different species, are generally quite elongated, and are composed of numerous branches, or acini, much like a bunch of grapes in form, all of which connect with a longitudinal *vitelloduct* (one on each side of the body); these longitudinal ducts are in turn connected by a pair of transverse ducts which unite in the median line, immediately posterior of the shell-gland, to form a common reservoir; this, in turn, empties into the ootype through the short vitelloduct mentioned above. The vitellaria produce yolk cells, which are associated with the true ovum to form the eggs.

*Excretory system.*—At or near the posterior extremity, generally somewhat dorsally, is situated a small pore (*porus excretorius*), which leads into a *median terminal*

*vesicle*; this latter gives off longitudinal branches; these in turn give off secondary branches, which ramify through the body, each small branch ending in an excretory cell.

*Nervous system*.—A set of ganglia is found at each side of the pharynx; these ganglia are connected by a dorsal commissure and give off numerous nerves to various parts of the body. The largest nerves are the two ventral longitudinal nerves which run antero-posteriorly, and can frequently be seen in fresh specimens.

*Life history*.—See p. 23.

KEY<sup>a</sup> TO THE GENERA OF TREMATODA REPORTED FOR MAN.

(For species parasitic in man and thus far found in the United States, follow roman type.)

- |  |                             |
|--|-----------------------------|
| 1. Two suckers (acetabula) present.....  | 2                           |
| One sucker (acetabulum) present (Monostomidæ).....   | <i>Monostomulum</i> (p. 12) |
| 2. Ventral acetabulum on ventral surface of anterior half of body.....                               | 3                           |
| Ventral acetabulum at posterior end of body, terminal or subterminal ( <i>Paramphistomidæ</i> )..... | <i>Gastrodiscus</i> (p. 45) |
| 3. Monecious (hermaphrodites) ( <i>Fasciolidæ</i> ).....   | 4                           |
| Diecious (sexes separated) ( <i>Schistosomidæ</i> ).....   | <i>Schistosoma</i> (p. 50)  |

FASCIOLIDÆ.

- |   |                              |
|---|------------------------------|
| 4. Mature distomes, or worms developed at least to a stage which permits a determination of the genus.....  | 5                            |
| Immature distomes, or forms not sufficiently developed to permit a determination of the genus.....  | <i>Agamodistomum</i> (p. 12) |
| 5. Genital pore not surrounded by a circular, muscular, acetabulum-like structure.....  | 6                            |
| Genital pore postero-lateral of acetabulum and surrounded by a circular, muscular structure which looks like a third acetabulum.....                | <i>Heterophyes</i> (p. 43)   |
| 6. Genital pore between oral sucker and acetabulum.....   | 7                            |
| Genital pore postero-median or postero-lateral of acetabulum.....   | <i>Paragonimus</i> (p. 15)   |
| 7. Intestinal ceca dendritic.....   | <i>Fasciola</i> (p. 21)      |
| Intestinal ceca not dendritic.....  | 8                            |
| 8. Body large, usually over 25 mm. long, and 14 mm. broad; ovary branched; vitellogene glands extend to posterior end of body, caudad of testicles. |                              |
|   | <i>Fasciolopsis</i> (p. 39)  |
| Body usually less than 20 mm. long, and rarely over 5 mm. broad; ovary not branched; vitellogene glands do not extend caudad of testicles....       | 9                            |
| 9. Testicles anterior of ovary and uterine coils.....   | <i>Dicrocoelium</i> (p. 28)  |
| Testicles posterior of ovary and uterine coils.....   | <i>Opisthorchis</i> (p. 30)  |

<sup>a</sup>This key is based primarily upon the species found in man, and on this account should not be relied upon for other species found in other animals.



## OPHTHALMIC DISTOMATOSIS.

On only two occasions have trematodes been reported for the human eye, but neither of the parasites is well described. For a full discussion of these cases, with English translations of the original observations, also with bibliography and synonymy, see Stiles (1902, pp. 24-35, pl. 3, figs. 2-5). Cases of similar infection are described for fish.

### Family MONOSTOMIDÆ.

Collective group MONOSTOMULUM Brandes, 1892.

GENERIC DIAGNOSIS.—Monostomidæ: An artificial collective group to contain agamic monostomes in which the characters are not sufficiently developed to permit of an exact generic determination. Such an artificial group does not have any type species.

The Eye Monostome—MONOSTOMULUM LENTIS<sup>a</sup> (Gescheidt, 1833) Brandes, 1892—of Man.

[No illustrations published.]

SPECIFIC DIAGNOSIS.—*Monostomulum*: One-tenth of a line (0.22 mm.) long.

HABITAT.—In crystalline lens of eye of man (*Homo sapiens*), in Odessa.

### Family FASCIOLIDÆ.

Collective group AGAMODISTOMUM<sup>b</sup> Stossich, 1892.

GENERIC DIAGNOSIS.—Fasciolidæ: An artificial collective group to contain agamic distomes in which the characters are not sufficiently developed to permit of an exact generic determination. Such an artificial group does not have any type species.

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<sup>a</sup> SYNONYMS.—? *Fasciola hepatica* Linnæus, 1758 [see p. 22]; "Monostomen" Nordmann, 1832; *Monostoma lentis* Gescheidt, 1833; *Monostomum lentis* (Gescheidt, 1833) Diesing, 1850; *Festucaria lentis* (Gescheidt, 1833) Moquin-Tandon, 1860; "Distoma ophthalmobium Diesing, 1850" of Cobhold, 1864, in part; *Monostomulum lentis* (Gescheidt, 1833) Brandes, 1892; ? *Agamodistomum ophthalmobium* [see p. —]; ? *Dicrocoelium lanceatum* Stiles & Hassall, 1896 [see p. —].

<sup>b</sup> SYNONYMS.—*Agamodistomum* Stossich, 1892; *Distomulum* Brandes, 1892; *Agamodistoma* Stossich, 1898.





1

2



3

4

Haines, del.

DORSAL AND VENTRAL VIEWS OF AGAMODISTOMUM OPHTHALMOBIUM.

FIG. 1. Ventral view of *Agamodistomum ophthalmobium*. (After von Ammon, 1833, pl. 12, fig. 24.)

FIG. 2. "Dorsal" (lateral?) view of same. (After von Ammon, 1833, pl. 12, fig. 25.)

FIGS. 3, 4. Two other views of same in different stages of contraction. (After von Ammon, 1841, pl. 14, figs. 19, 20.)

Note that in fig. 1, published in 1833, a ventral acetabulum is distinct; in figs. 3 and 4, published in 1841, no ventral acetabulum is evident.



The Eye Distome—AGAMODISTOMUM OPHTHALMOBIUM<sup>a</sup> (Diesing, 1850)  
Stossich, 1892—of Man.

[Figs. 1 to 4.]

SPECIFIC DIAGNOSIS.—*Agamodistomum*: Body ovate-lanceolate, variable, one-fourth to one-half line long, one-sixth of a line broad. Mouth terminal to subterminal, orbicular. Acetabulum one-third larger than oral sucker, subcentral, with circular aperture.

HABITAT.—Between crystalline lens and its capsule, in eye of man (*Homo sapiens*), in Dresden.

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<sup>a</sup>SYNONYMS.—“Distomen” Ammon, 1833; *Distoma oculi humani* Gescheidt, 1833; *Distomum ophthalmobium* Diesing, 1850; *Distoma ophthalmobium* (Diesing, 1850) Küchenmeister, 1855; *Dicrocalium oculi humani* (Gescheidt, 1833) Weinland, 1858; “*Distoma oculare* Nordmann” of Moquin-Tandon, 1860; *Fasciola ocularis* Moquin-Tandon, 1860; *Fasciola oculis* Moquin-Tandon, 1861; *Distoma ocular* de Bonis, 1882; *Agamodistomum ophthalmobium* (Diesing, 1850) Stossich, 1892; ?*Dicrocalium lanceatum* Stiles & Hassall, 1896 [see p. 29]; “*Distom. okuli humani* Ammon” of Schneidemühl, 1896.

## PULMONARY DISTOMATOSIS OR PARASITIC HEMOPTYSIS AND CEREBRAL DISTOMATOSIS OR JACKSONIAN (CORTICAL) EPILEPSY.

Pulmonary distomatosis is the primary, cerebral distomatosis the secondary infection, and while it is not excluded that cerebral infection may take place in connection with hepatic or venal infection, still



FIG. 9.—Section of a cyst in the lower lobe of a cat's left lung containing two lung flukes. *A, B*, cross-sections of the two worms; *a, a*, parenchyma of the worms; *b, b*, cuticle, with spines; *c, c*, intestinal ceca; *d*, a part of the ovary; *e*, vitellaria; *f*, shell gland; *g*, eggs in the uterus; *h*, cyst wall; *i*, flattened epithelial cells forming the lining of the cyst; *j*, schlemm glands in the wall of the cyst.  $\times 11$ . (After Katsurada, 1900, pl. 14, fig. 1.)

as a matter of fact it has been reported only in Asia, where it occurs in connection with *Paragonimus*-infection of the lungs. The parasites are also recorded for the liver, peritoneum, testicles, etc.

CLINICAL DIAGNOSIS.—Examine fresh unstained sputum for eggs (figs. 11-12).

SYMPTOMS.—Cough, spitting of tenacious, rusty, or bloody sputum; in cerebral infection, also epileptic attacks.



5

LUNGS OF SWINE INFECTED WITH FLUKES.

FIG. 5. The lungs of a hog, showing the cysts caused by infection with lung flukes (*Paragonimus westermanii*). Reduced. (After Stiles & Hassall, 1900, pl. 23.)







6



7



8

LUNG FLUKES OF SWINE.

FIG. 6. A portion of hog's lung, containing a lung-fluke cyst, which is here cut open. (After Stiles & Hassall, 1900, pl. 24, fig. 1.)

FIG. 7. Six lung flukes (*Paragonimus westermanii*) from hogs. Drawn from life; slightly reduced; natural color. (After Stiles & Hassall, 1900, pl. 24, fig. 2.)

FIG. 8. Content of a lung-fluke cyst, containing eggs of the lung fluke. Greatly magnified. (After Stiles & Hassall, 1900, pl. 24, fig. 3.)



TREATMENT.—Send patient to noninfected region, thus preventing reinfection; specific treatment unknown.

For a detailed discussion of this subject, with review of the medical literature, see Stiles & Hassall (1900, pp. 560–611).



FIG. 10.—Section of a cyst in the lower lobe of the left lung of a man containing a lung fluke. *A*, diagonal section of the worm; *a*, parenchym; *b*, cuticle, with spines; *c*, intestinal ceca; *d*, testicles; *e*, vitellaria; *f*, eggs in the uterus; *g*, ventral acetabulum; *h*, excretory system; *i*, cyst wall; *j*, cylinder epithelium in part ciliated.  $\times 12$ . (After Katsurada, 1900, pl. 14, fig. 2.)

### Family FASCIOLIDÆ.

#### Genus PARAGONIMUS<sup>a</sup> Braun, 1899.

GENERIC DIAGNOSIS.—Fasciolide: Body medium large, thick, elongate, frequently oval, and on cross section more or less round, usually somewhat attenuate toward posterior extremity. Cephalic cone wanting. Skin provided with scale-like spines. Acetabulum near equator. Intestine with strong, somewhat elongate pharynx; very short esophagus; intestinal ceca zigzag, extending to caudal end of the body. Median excretory stem (or bladder) large dorso-ventrally, irregular in outline, and extending cephalad to near the pharynx. Genital pore near caudal margin of ventral acetabulum, in median line or to the right or left. Copulatory organs (cirrus) absent. *Male organs*: Testicles round (?), or branched, in posterior half of body, one each side of median line and one slightly posterior of the other. *Female organs*: Ovary somewhat branched, the branches being thick and short, and the organ located postero-

<sup>a</sup>SYNONYMS.—*Paragonimus* Braun, 1899; *Polysarcus* Looss, 1899 [not Fieb., 1853, orthopteron.]

lateral of the ventral acetabulum, on the side (right or left) of the median line opposite to the main portion of the uterus; receptaculum seminis absent; Laurer's canal present; vitellaria enormously developed, extending from anterior to posterior end of the body and located (as seen in cross section) on the periphery, usually leaving a longitudinal free space both in the dorsal and ventral median field. The transverse vitelloducts pass cephalad of the testicles, but caudad of ovary and uterus. Uterus may be only slightly developed, or may form a comparatively large-sized rosette more than half as broad as the body; it may be located entirely on one side (right or left) of median line, or may extend both sides of median



FIG. 11.—Sputum of man containing eggs of the lung flukes, greatly enlarged. (After Manson, 1900, p. 568, fig. 84.)

line, partially covering the ovary. Eggs rather large, about 80 to 118  $\mu$  long by 48 to 60  $\mu$  broad. Embryo develops after oviposition.

HABITAT.—Encysted, usually two in each capsule, in lungs of mammals.

TYPE SPECIES.—*Paragonimus westermanii* (Kerbert, 1878).

The Asiatic Lung Fluke—**PARAGONIMUS WESTERMANII** <sup>a</sup> (Kerbert, 1878) Stiles & Hassall, 1900—of Man.

[Figs. 5 to 16.]

SPECIFIC DIAGNOSIS.—*Paragonimus*: 8 to 16 mm. (after Kellicott 15 to 20 mm.) long, 4 to 8 mm. broad, 2 to 5 mm. thick; plump, pinkish to reddish-brown (alive) or slate (preserved) in color; live specimens are depressed and with variable outline; preserved specimens often oval to elongate pyriform, transverse section round or nearly so, anterior end bluntly rounded, posterior end less blunt. Oral sucker 0.53 to nearly 0.75 mm. (Leuckart) or more (0.864 by 1.017 mm. or 1 to 1.4 mm.)<sup>b</sup> (Ward); or 0.80 to 1.12 by 0.80 to 0.83 mm. (Stiles & Hassall); 0.78 (Kerbert) in

<sup>a</sup> SYNONYMS.—*Distoma westermanii* Kerbert, 1878; *Distoma ringeri* Cobbold, 1880; *Gregarina pulmonum* Baelz, 1880; *Gregarina fusca* Baelz, 1880; *Distomum westermani* Kerbert, 1881; *Distoma pulmonis* Kiyona, Suga, and Yamagate (1881!); *Distomum pulmonis* Kiyona, Suga, and Yamagate (1881); *Distoma pulmonale* Baelz, 1883; *Distoma pulmonar* La Clinica de Malaga, 1883; *Distoma pulmonum* (Baelz) Tomono Hidekata, 1883; "*Distoma hepaticum* Linn." of Miura, 1889; *Distomum ringeri* (Cobbold, 1880) von Linstow, 1889; *Distomum westermani* Leuckart, 1889; *Distomum pulmonale* (Baelz) Leuckart, 1889; *Distomum cerebrale* Yamagiwa, 1890; *Distoma ringers* Rev. Sci., 1890; "*Mesogonimus westermani* (Kerbert, 1878)" Railliet, 1890; *Mesogonimus pulmonalis* (Baelz, 1883) Railliet, 1890; *Mesogonimus ringeri* (Cobbold, 1880) Railliet, 1890; *Distoma westermani* (Kerbert, 1881) Weber, 1891; "*Distoma westermani* (Leuckart) Blanchard, 1891; "*Mesogonimus pulmonale* (Baelz, 1878)" Stossich, 1892; "*Distoma* (*Mesogonimus*) *westermani* Kerbert, 1878," of Stiles, 1894; *Distomum* sp. of Kellicott, 1894; *Distomi ringeri* (Cobbold, 1880) Simon, 1897; *Paragonimus westermanii* (Kerbert, 1878) Stiles & Hassall, 1900.

<sup>b</sup> Suckers distorted, measurements not exact.—Ward.



diameter, terminal or subterminal in different specimens from the same lung. Ventral acetabulum (0.6 to at most 0.75 mm.—Leuckart; 0.78 mm.—Kerbert; 0.75 to 1.017 mm.—Ward; 0.88 to 1.2 by 0.86 to 1.44 mm.—Stiles & Hassall) very slightly larger than oral sucker; situated somewhat anterior of equator of the body, 2 to 4 mm. back of oral sucker. Skin provided with broad scale-like spines.<sup>a</sup> Pharynx elongate; esophagus very short, so that the bifurcation of the intestine is considerably anterior of the ventral acetabulum; intestinal ceca usually somewhat zigzag, some distance from each other, run

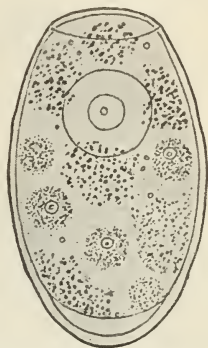


FIG. 12.—Egg of the lung fluke showing the ovicell and a number of vitelline or yolk cells. Note also the cap or operculum.  $\times 1,000$ . (After Katsurada, 1900, p. 507, fig. 3.)

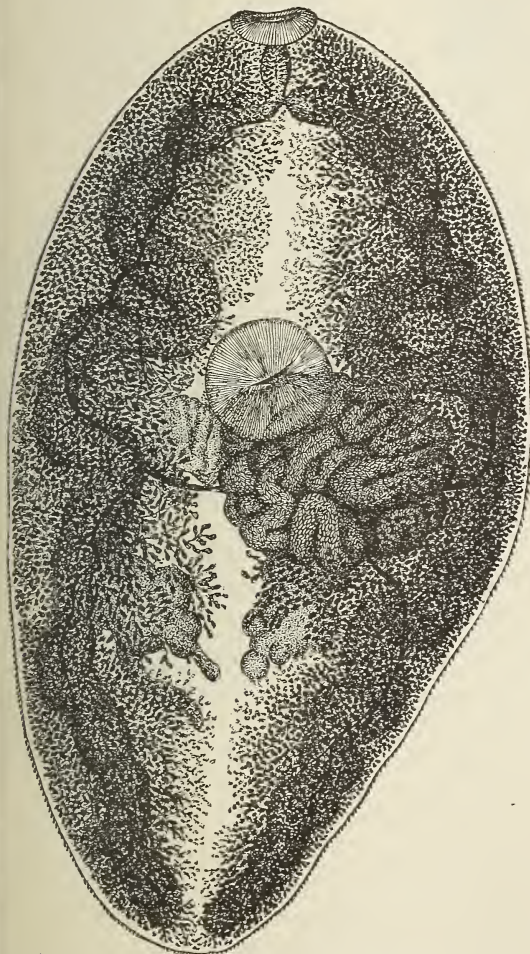


FIG. 13.—Ventral view of a compressed specimen of a lung fluke from a hog. Greatly enlarged. (After Stiles & Hassall, 1900, p. 563, fig. 24.)

irregularly to posterior extremity. *Genital pore*, often indistinct, close to the caudal margin of ventral acetabulum, may be in the median line or immediately to the right or left of it. *Male organs*: Cirrus and cirrus pouch absent; ductus ejaculatorius straight; testicles tubular, ramified, one slightly posterior of other, on each side of median line. *Female organs*: Ovary branched, lateral, right or left of median line, somewhat posterior of acetabulum and antero-ventral of transverse vitello-duct; on the opposite side of median line, at about the same height, is situated a lobate shell gland and a rather short, massed uterus; in some specimens the latter may spread across the median line and partially cover the ovary; folds of uterus extend ventrally of shell gland; vitellaria marginal, highly developed, extending from anterior to posterior extremity, often leaving but a

small portion of the dorsal and ventral median field uncovered; transverse vitello-ducts dorsal; vitelline reservoir large; Laurer's canal present. *Eggs* oval, 80 to 100  $\mu$

<sup>a</sup> Largest in the middle of the body, after Leuckart, but largest on anterior portion, after Kerbert; smallest around mouth, after Stiles & Hassall.

long by  $56 \mu$  broad (Leuckart); 96 to  $118 \mu$  long by 48 to  $53 \mu$  broad (Ward); 68 to  $96 \mu$  long by 48 to  $60 \mu$  broad (Stiles & Hassall); yellow shell. Miracidium ciliated, develops after eggs leave the host. Sporocyst, redia, cercaria, and intermediate host undetermined.

HABITAT.—Lungs and brain (occasionally in other parts of the body), royal tiger (*Felis tigris*), domesticated cat (*Felis catus domestica*), domesticated dog (*Canis familiaris*), swine (*Sus scrofa domestica*), and man (*Homo sapiens*).

GEOGRAPHIC DISTRIBUTION.—China, Japan, Formosa, occasional imported cases in Europe, some cases of endemic infection in the United States.

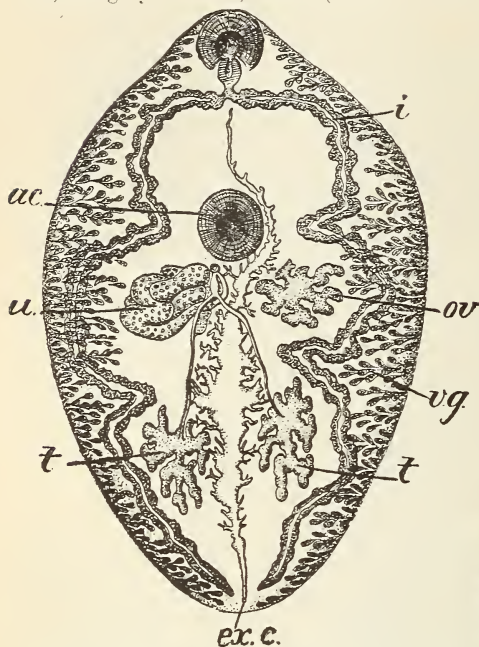


FIG. 14.—Ventral view of a lung fluke from man showing anatomy: *ac*, acetabulum; *ex. c.*, excretory canal; *i*, intestinal ceca; *ov.*, ovary; *t*, testicles. (After Leuckart, 1889, p. 405, fig. 182.)

From the medical point of view this is one of the most important flukes, but from the agricultural standpoint

it is less important than *Fasciola hepatica* (see p. 22). Thus far the Asiatic lung fluke has been reported for this country for the cat (at Ann Arbor, Mich.), the dog (at Columbus, Ohio), and the domesticated hog (at the abattoirs in Cincinnati, Ohio). One (imported) case in man has recently been found in Portland, Oreg. It should be held in mind in connection with American troops who return from service in the Philippines.



FIG. 16.—Egg of the lung fluke from man containing a ciliated embryo, and showing the cap or operculum at one end. (After Nakahama, 1883.)

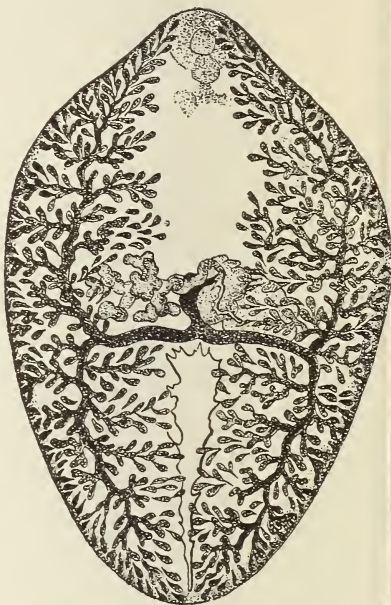


FIG. 15.—Dorsal view of a lung fluke from man showing ovary, shell gland, vitellaria, and Laurer's canal. (After Leuckart, 1889, p. 186, fig. 428.)

Genus *FASCIOLA* Linnæus, 1758.

For diagnosis, see p. 21.

Although pulmonary distomatosis is usually caused by flukes of the genus *Paragonimus*, it occasionally happens that the liver flukes (genus *Fasciola*) are found in the lungs of various animals. One case of such infection in man has been reported. The species in question was—



The Giant Liver Fluke—*FASCIOLA GIGANTICA* <sup>a</sup> Cobbold, 1856—of Giraffes, Cattle, Sheep, Goats, and Man.

[Figs. 17 to 18.]



FIG. 17.—The Giant Liver Fluke (*Fasciola gigantica* [*F. hepatica aegyptiaca*]), drawn from one of Looss's specimens, natural size. (After Stiles, 1898, p. 49, fig. 25.)

SPECIFIC DIAGNOSIS.—*Fasciola*: 25 to 75 mm. long by 3 to 12 mm. broad, flat, oblong, lanceolate; anterior end cylindrical, attenuate; sides nearly parallel for greater part of length, especially of the anterior half; posterior end obtuse. Oral sucker 1.12 mm. in diameter; ventral acetabulum somewhat larger. Skin with spines. Pharynx, —?—; esophagus extends nearly to acetabulum; intestinal caeca more profusely branched than in *F. hepatica*. Genital pore median, about halfway between mouth and acetabulum.

*Male organs*: Similar to those of *F. hepatica*, but the testicles are more profusely and delicately branched and do not extend so far caudad. *Female organs*: In general similar to those of *F. hepatica*, but more profusely and delicately branched. *Eggs*, 150 to 190  $\mu$  long by 75 to 90  $\mu$  broad. Sporocyst, redia, cercaria and intermediate host undetermined.

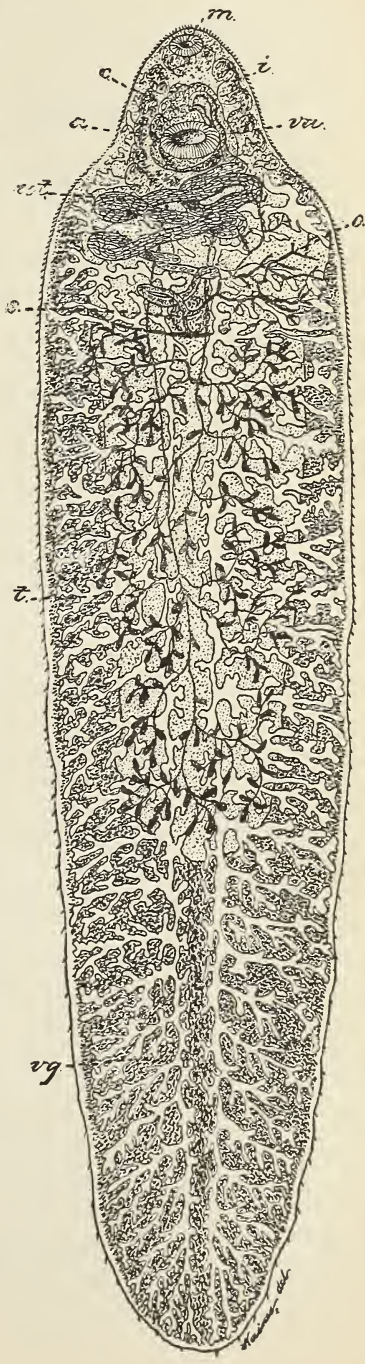
HABITAT.—Liver of giraffe (*Giraffa camelopardalis*), cattle (*Bos taurus*), zebu (*Bos indicus*), buffalo (*Bos bubalis*), sheep (*Ovis aries*), goats (*Capra hircus*), in Africa. One case reported for lungs of man (*Homo sapiens*).

<sup>a</sup>VERNACULAR NAMES.—The giant liver fluke; the narrow liver fluke; the Egyptian liver fluke.

SYNONYMS.—*Fasciola gigantica* Cobbold, 1856; *Distomum giganteum* Diesing, 1858; *Distoma hepaticum* (in part) of Gervais & van Beneden, 1859; *Fasciola gigantea* (Diesing) Cobbold, 1858; *Cladocelium giganteum* (Diesing) Stossich, 1892, in part; *Fasciola hepatica angusta* Railliet, 1895; *Fasciola hepatica aegyptiaca* Looss, 1896; *Fasciola angusta*.

BIBLIOGRAPHY.—For bibliography and technical discussion, see Stiles (1895, pp. 139-143); Looss (1902, pp. 782-783).

FIG. 18.—The Giant Liver Fluke (*Fasciola gigantica* [*F. hepatica aegyptiaca*]), enlarged to show the anatomic characters: *ac*, acetabulum; *c*, *g*, cirrus pouch; *i*, intestinal caecum; *m*, mouth, with oral sucker; *ov*, ovary; *s*, *g*, shell gland; *t*, profusely branched testicles; *ut*, uterus; *va*, vagina; *v*, *g*, profusely branched vitellogenic glands. (After Looss, 1896, pl. 3, fig. 16.)



## HEPATIC DISTOMATOSIS.

At least five species of parasites have been reported in connection with hepatic distomatosis in man; all are members of the family Fasciolidae.

CLINICAL DIAGNOSIS.—Make microscopic examination of fresh, unstained feces for eggs; also, examine sputum and urine for eggs, as the ova in pulmonary and venal distomatosis may be discharged per anum; hence, finding eggs in feces without excluding distomatosis of lungs and veins may lead to error in diagnosis (see pp. 14, 49).

SYMPTOMS.—Best studied for epizootic distomatosis caused by *Fasciola hepatica* in sheep: (1) Period of traumatic inflammation of liver, symptoms may be indefinite, no eggs in feces; (2) period of anemia, positive diagnosis may be made by finding characteristic eggs in feces; (3) period of emaciation, atrophy of liver; (4) period of emigration of flukes. For more detailed discussion in English, see Stiles (1898, pp. 29-57).

Taylor (1884, pp. 48-57) gives the following symptoms for infection of man with *Opisthorchis sinensis*:

The dwellers in these villages are attacked irrespective of age, sex, or physical condition. Young children are among the sufferers. When one in a family is found infected, several members of the family generally present the same symptoms in a greater or less degree. In this respect this disease offers a contrast to Endemic Hæmoptysis. A very large ratio of the inhabitants of the villages mentioned are victims of the parasite. Some native practitioners place the estimate at 1 in every 7, while others make it as high as 1 in every 5 of the whole population.

*Symptoms and course.*—One of the first and most prominent symptoms is the enlargement of the liver, followed, attended, or preceded by diarrhoea. At first the diarrhoea is irregular and intermittent, the attacks gradually become more frequent and lasting longer, till, after a period of from 2 to 5 years, there may be hardly any interval between them. The stools, which may or may not be dark and bloody, sometimes reach 12 in a day. In some cases bloody diarrhoea becomes after a time almost constant, while in others blood appears in the stools only at irregular intervals. The liver continues to increase in size, though at times it apparently diminishes temporarily. There may be occasional tenderness over the hepatic region, or more or less constant pain. Jaundice, sometimes intermittent, is a frequent symptom. There is generally a dark ashen discoloration of the skin. The temperature varies between 99° and 100.5° F., or may remain normal. The pulse, though generally about normal, frequently rises to 85° or 100°. After a time anasarca, likewise intermittent, appears and affects the legs especially. Ascites is also very likely to

occur, increase for a time, and then gradually diminish, to appear again and again. The patient is reduced by diarrhoea, becomes emaciated, and grows anæmic and weak, but the appetite is usually preserved. Thus it happens that the victims of this disease are frequently reduced so low that their life is despaired of, yet they gradually recover and become apparently almost well. By and by, however, relapse occurs, and the same process is repeated again and again, ground being lost on each occasion, until at length, worn out by exhaustion, the patient after many years of illness dies. Whether any fully recover is not stated, or whether a change of locality is attended by continuous convalescence is not yet known. Recovery after becoming the victim of *Distoma hepaticum* [*O. sinensis*] must at best be problematic. When in an affected locality a case of enlargement of the liver and diarrhoea presents itself, careful examination of the feces is generally rewarded by finding the ova of the *Distoma*.

Many of these patients are troubled with skin diseases, but being of a poor class and living in a more or less filthy condition the skin disease may have no connection with the diseased liver.

**TREATMENT.**—No specific treatment; remove patient to noninfected area, or if kept at home avoid further infection and give nourishing food. Salol has recently been reported as effective in liver-fluke disease in sheep, but the results obtained are not yet published in sufficient detail to permit of a satisfactory opinion.

### Family FASCIOLIDÆ.

Genus FASCIOLA <sup>a</sup> Linnæus, 1758.

**GENERIC DIAGNOSIS.**—Fasciolidæ: Body quite large, broad, and flat; the anterior portion differentiated into a conical cephalic cone, and usually quite well defined from the broader, flatter, leaf-like portion. Skin provided with strong spines. Acetabulum near base of cephalic cone, and of about the same size as the oral sucker. Intestine with well-developed pharynx, short esophagus, and long intestinal ceca; the latter extend to the extreme aboral pole of the body, and are provided with numerous long lateral and fewer and shorter median branches; these branches may branch secondarily. Excretory system highly developed. *Genital pore* median at base of cephalic cone, and anterior of ventral acetabulum. Copulatory organs present, genital glands about in the middle of the body. *Male organs*: Testicles side by side or one diagonally posterior of the other, both caudad of the ovary and transverse vitelloduct, and profusely branched. *Female organs*: Ovary lateral of median line, anterior of transverse vitelloduct, posterior of acetabulum, profusely branched. Receptaculum seminis absent; Laurer's canal present. Vitellaria very profusely developed, extending from base of cephalic cone to extreme aboral pole, and occupying nearly the entire posterior portion of body, especially the margins except the portion occupied by the testicles, ovary, and uterus; uterine coils form a rosette between testicles and acetabulum. *Eggs* not especially numerous, but large, with development after oviposition.

**HABITAT.**—Liver of mammals, especially herbivorous animals.

**TYPE SPECIES.**—*Fasciola hepatica* Linnæus, 1758, of ruminants.

<sup>a</sup> **SYNONYMS.**—*Fasciola* Linnæus, 1758; *Planaria* Gœze, 1782 (not Mueller, 1776); *Distoma* Retzius, 1782 (not Savigny, 1816); *Distoma* (*Cladocalium*) Dujardin, 1845; *Fasciolaria* Anonymous, 1845; *Distomum* Diesing, 1850; *Cladocalium* Pontallié, 1853; *Distomum* (*Fasciola*) Leuckart, 1863; *Cladocalium* (Dujardin) Stossich, 1892; *Phasciola* Wilder, 1894.



The Common Liver Fluke—*FASCIOLA HEPATICA* *a* Linnæus, 1758—of Ruminants, Man, etc.

[Figs. 19 to 38.]

**SPECIFIC DIAGNOSIS.**—*Fasciola*: 18 to 51 mm. long, 4 to 13 mm. broad; pale brown to slate in color; the anterior 3 to 5 mm. forms a rather thick conical portion which is more or less distinctly defined from the broad, flat, leaf-like body of elongate-oval form; this latter widens rapidly to the maximum breadth, then decreases gradually in width to the posterior end, which is bluntly pointed. Oral sucker about 1 mm. in diameter, round, terminal, but inclines ventrad. Ventral acetabulum about 1.6 mm. in diameter, situated about 3 to 4 mm. caudad of oral sucker. Skin provided with numerous spines placed side by side in alternating rows extending ventrally as far as the posterior border of the testicles, but dorsally not so far; smaller on the cephalic cone than on the body. Pharynx elongate 0.7 mm. long; esophagus 0.4 mm. broad, rarely over 1 to 1.5 times as long as the pharynx, so that the bifurcation of the intestine is immediately anterior of the genital pore; intestinal ceca dendritic, some branches extending into the cephalic cone, and the posterior end of the ceca extending to caudal extremity of worm; lateral branches longer, much more profuse, and more numerous than median branches. Genital pore median, about halfway



FIG. 19.—The Common Liver Fluke (*Fasciola hepatica*), natural size. (After Stiles, 1898, p. 29, fig. 2.)

between the oral sucker and acetabulum. *Male organs*: Cirrus frequently found extruded from pore, and then recurved; cirrus pouch present, containing pars prostatica and vesicula seminalis; testicles profusely branched, situated for the greater part caudad of the transverse vitelloduct. *Female organs*: Vulva at side of cirrus; uterus forms a rosette with numerous coils, and is frequently visible to the naked eye as a dark-brown spot immediately posterior of the ventral acetabulum; ovary branched and anterior of the transverse vitelloduct; vitellaria profusely branched and occupy the entire margin of the body from the acetabulum to the posterior extremity; they lie dorsally as well as ventrally of the intestine, and become broader posteriorly. Excretory system highly developed. *Eggs* (fig. 21) oval, 130 to 145  $\mu$  long by 70 to 90  $\mu$  broad; miracidium (figs. 22–23) conical, ciliated, with oral papilla, two cup-shaped eye-spots, and rudimentary intestine; metamorphosis (sporocyst, redia, cercaria)

takes place in small snails of the genus *Limnæa* (*L. truncatula* and others, figs. 34–38); cercaria (fig. 23) whitish, owing to excessive development of the capsule glands, encysts upon plants.

**HABITAT.**—Gall ducts, occasionally lungs, or other portions of the body of cattle (*Bos taurus*), sheep (*Ovis aries*), swine (*Sus scrofa domestica*), and other mammals; rare in man (*Homo sapiens*).

*a* **VERNACULAR NAMES.**—English, *Common Liver Fluke*; German, *Leberegel*, *Leberwurm*, *Schafegel*; Dutch, *Botten*, *Leverwurm*; Danish, *Færeflynder*; Swedish, *Levermask*; French, *Douve hépatique*, *fasciola*; Italian, *biscuola*, *distoma epatico*; Spanish, *caracolillo*.

**SYNONYMS.**—*Fasciola hepatica* Linnæus, 1758; *Planaria latiuscula* Gœze, 1782; *Distoma hepaticum* (Linnæus) Abildgaard (?); *Fasciola humana* Gmelin, 1790; *Distoma* (*Cladocalium*) *hepaticum* (Linnæus) of Dujardin, 1845; *Fasciolaria hepatica* (Linnæus) Anonymous, 1845; *Distomum hepaticum* (Linnæus) Diesing, 1850; *Distomum* (*Fasciola*) *hepaticum* Linnæus of Leuckart, 1863; *Cladocalium hepaticum* (Linnæus) Stossich, 1892.

**BIBLIOGRAPHY.**—For bibliography, see Hassall (1894) and Huber (1894). For more technical discussion of this species, see Leuckart (1889, pp. 179–328).

For a summary of the 32 cases thus far reported for man see Blanchard, 1888a, pp. 589–595; Leuckart, 1889, pp. 313–328, or Moniez, 1896, pp. 103–111. For a general discussion of this parasite in English, see Stiles, 1898, pp. 29–48.

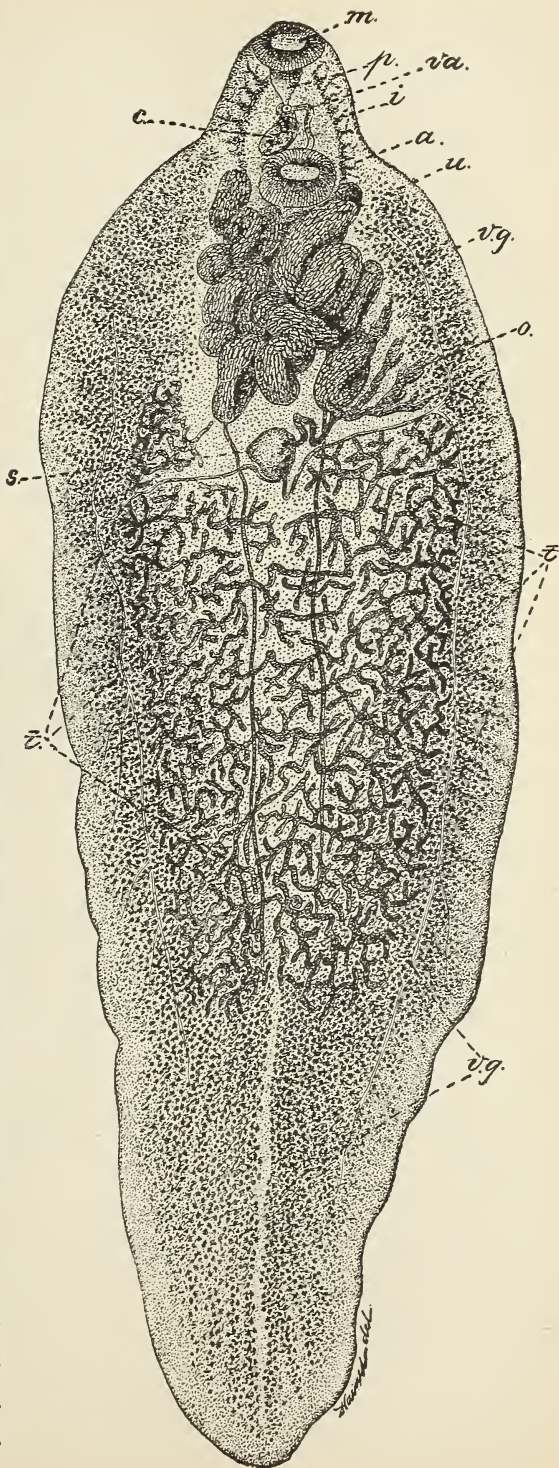
This worm is very common in Europe and not uncommon in the United States. From an agricultural standpoint it is the most important of the flukes, but from a standpoint of human medicine it is much less important than several other forms, notably *Paragonimus*, *Opisthorchis*, and *Schistosoma*.

**LIFE HISTORY.**—As an example of the life history of flukes, we may take that of *Fasciola hepatica*, which may be summarized as follows:

(a) The *adult hermaphroditic worm* (figs. 19-20), the characters of which are given on p. 22, fertilizes itself or a cross fertilization of two individuals takes place in the biliary passages of the liver, and produces a large number (estimated at 37,000 to 45,000) of eggs.

(b) *Eggs* (figs. 21 and 22).—Each egg is composed of the following parts: (1) A true germ cell, which originates in the ovary and is destined to give rise to the future embryo; (2) a number of vitelline or yolk cells, which are formed in a

Fig. 20.—The Common Liver Fluke (*Fasciola hepatica*), enlarged to show the anatomic characters: *ac*, acetabulum; *c. p.*, cirrus pouch; *i*, intestinal ceca; *m*, mouth with oral sucker; *ov*, ovary; *p. b.*, pharyngeal bulb; *s. g.*, shell gland; *t*, profusely branched testicles; *ut*, uterus; *va*, vagina; *vg*, profusely branched vitellogene gland. (After Stiles, 1894, p. 300.)





specialized and independent portion (vitellogene gland) of the female glands; instead of developing into embryos, the yolk cells form a follicle-like covering for the true germ cell and play an important rôle in the nutrition of the latter as it undergoes

further development; (3) a shell surrounding the germ cell and the vitelline cells, and provided at one end with a cap or operculum. The eggs escape from the uterus of the adult through the vulva, are carried to the intestine of the host with the bile, then pass through the intestines with the contents of the latter, and are expelled from the host with the fecal matter. Many of them become dried and then undergo no further development, but others are naturally dropped in the water in marshes, or, being dropped on dry ground, they are washed into the water by the rain, or are carried to a more favorable position by the feet of animals pasturing in or passing through the fields. After a longer or shorter period of incubation, which varies with the temperature, a ciliated embryo

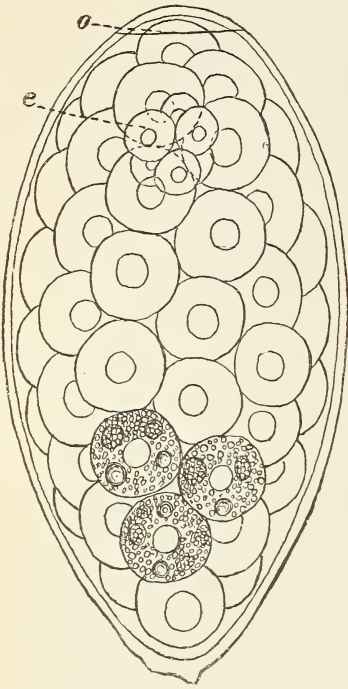


FIG. 21.—Egg of the Common Liver Fluke (*Fasciola hepatica*) examined shortly after it was taken from the liver of a sheep; at one end is seen the lid or operculum, *o*; near it is the segmenting ovum, *e*; the rest of the space is occupied by yolk cells which serve as food; all are granular, but only three are thus drawn.  $\times 680$ . (After Thomas, 1883, p. 281, fig. 1.)

(miracidium) is developed. At a temperature of  $20^{\circ}$  to  $26^{\circ}$  C. the miracidium may be formed in 10 days to 3 weeks; at a temperature of  $16^{\circ}$  C. the development takes 2 to 3 months; at  $38^{\circ}$  C. it ceases entirely. Experiments have shown that as long as these eggs remain in the dark the miracidium will not escape from the eggshell; accordingly it will not escape during the night. When exposed to the light, however, or when suddenly brought into contact with cold water, the organism bursts the cap from the eggshell, crawls through the opening and becomes a—

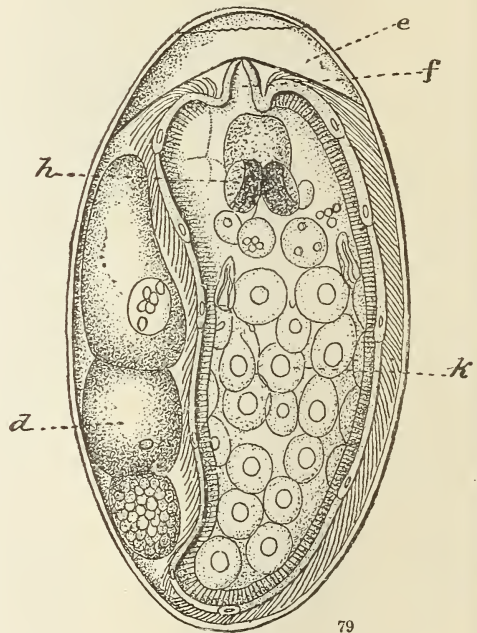


FIG. 22.—Egg of the Common Liver Fluke containing a ciliated embryo (miracidium) ready to hatch out: *a*, remains of food; *e*, cushion of jelly-like substance; *f*, boring papilla; *h*, eye-spots; *k*, germinal cells.  $\times 680$ . (After Thomas, 1883, p. 283, fig. 2.)

(c) *Free-swimming ciliated miracidium* (fig. 23).—As already stated, this organism is entirely different from its mother. It measures about 0.15 mm. long. It is somewhat broader in its anterior portion than in its posterior portion; on its anterior extremity we find a small eminence known as a boring papilla; the exterior surface of the young worm is covered with numerous cilia, which by their motion propel the animal through the water; inside the body we find in the anterior portion a simple vestigial intestine and a double ganglionic mass, provided with a peculiar pigmented double cup-shaped eye-spot; in the posterior portion of the body cavity is found a number of germ cells, which develop into individuals of the next generation.

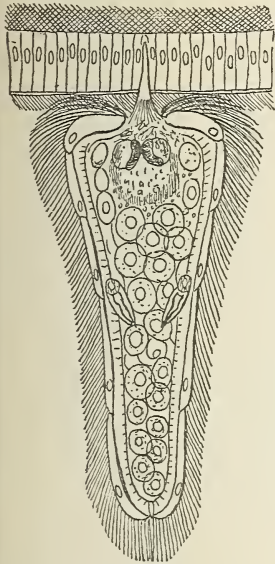


FIG. 23.—Embryo of the Common Liver Fluke (*Fasciola hepatica*) boring into a snail.  $\times 370$ . (After Thomas, 1883, p. 285, fig. 4.)

Swimming around in the water, the miracidium seeks out certain snails (*Limnaea truncatula*, *L. oahuensis*, *L. rubella*, see p. 38), which it immediately attacks (fig. 23). The miracidium elongates its papilla and fastens itself to the feelers, head, foot, or other exterior soft portions of

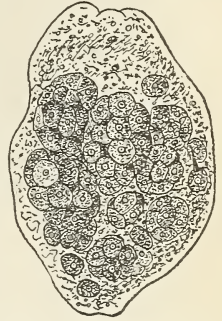


FIG. 24.—Sporocyst of the Common Liver Fluke which has developed from the embryo, and contains germinal cells.  $\times 200$ . (After Leuckart, 1889, p. 109, fig. 67 B.)

the body of the snail; some of the parasites enter the pallial (lung) cavity and attach themselves there. After becoming securely fastened to the snail the miracidium discards its ciliated covering and shortens to about half its former length (0.07 mm. to 0.08 mm.). The parasites now bore their way into the body of the snail and come to rest in the liver, or near the roof of the pallial cavity, etc., the movements gradually cease, and we have before us the stage known as the—

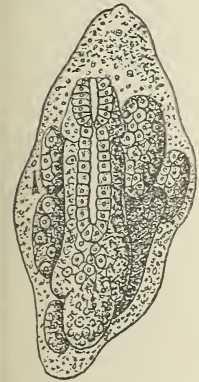


FIG. 25.—Sporocyst of the Common Liver Fluke, somewhat older than that of fig. 24, in which the germinal cells are giving rise to rediae.  $\times 200$ . (After Leuckart, 1889, p. 109, fig. 67 C.)

(d) *Sporocyst* (figs. 24 and 25).—The eye-spots, ganglionic swellings, and vestigial intestine become more and more indistinct and are finally lost. The sporocyst grows slowly at first, then more rapidly, and at the end of 14 days or so measures 0.5 mm. The germ cells mentioned as existing in the posterior portion of the miracidium now develop into individuals of the third generation known as—



FIG. 26.—Redia of the Common Liver Fluke (*Fasciola hepatica*), containing germinal cells which are developing into cercariae.  $\times 150$ . (After Leuckart, 1889, p. 269, fig. 129 A.)

(e) *Rediae* (figs. 26 and 27).—The rediae escape from the sporocyst when the latter is from 2 weeks (in summer) to 4 weeks

(in late fall) old. Upon leaving the body of the sporocyst they wander to the liver of the snail, where they grow to about 2 mm. long by 0.25 mm. broad. Each redia

consists of a cephalic portion, which is extremely motile and which is defined from the rest of the young worm by a ridge; under the latter is situated an opening through which the next generation (cercariæ) escapes. The posterior portion of the worm is provided at about the border of the third and last fourths of the body with two projections. There is a mouth with pharynx situated at the anterior extremity, the pharynx leading into a simple blind intestinal sac. The redia, as well as the sporocyst, may be looked upon as a female organism, and in its body cavity are found a number of germ cells, which develop into individuals of the next generation known as—



FIG. 27.—Redia of the Common Liver Fluke, with developed cercariæ.  $\times 150$ . (After Leuckart, 1889, p. 270, fig. 130.)

(*r*) *Cercariæ* (figs. 28-30).—These organisms are quite similar to the adult parasites into which they later develop. The body is flat, more or less oval, and provided with a tail inserted at the posterior extremity. The oral sucker and acetabulum are present as in the adult, but the intestinal tract is very simple; on the sides of the body are seen two large glands, but the complicated genital organs of the adult are not visible. The cercaria leaves the redia through the birth opening, remains in the snail for a longer or shorter time, or passes out of the body of the snail and swims around in the water.

After a time it attaches itself to a blade of grass (fig. 29) or some other object, and forms a cyst around itself with material from the large glands, at the same time



FIG. 28.—Free cercaria of the Common Liver Fluke, showing two suckers, intestine, large glands, and tail. (After Leuckart, 1889, p. 279, fig. 137.)

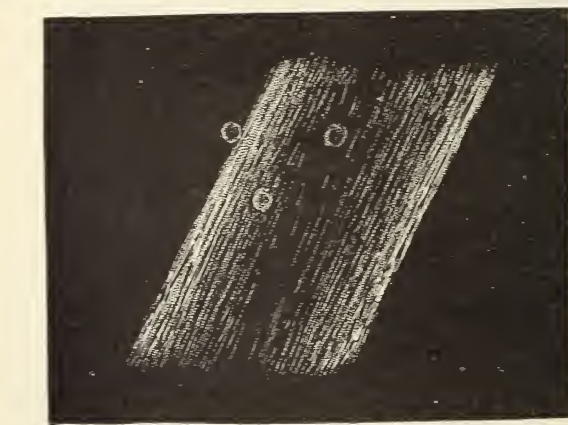


FIG. 29.—Portion of a grass stalk with three encapsuled cercariæ of the Common Liver Fluke (*Fasciola hepatica*).  $\times 10$ . (After Thomas, 1883, p. 291, fig. 13.)

losing its tail. It now remains quiet until swallowed by some animal. Then upon arriving in the stomach—of a steer, for instance—the cyst is destroyed, and the

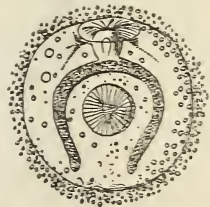


FIG. 30.—Isolated encysted cercaria of the Common Liver Fluke.  $\times 150$ . (After Leuckart, 1889, p. 286, fig. 142.)

young parasite wanders through the gall ducts, or, as some believe, through the portal veins to the liver, where it develops into the adult hermaphrodite.



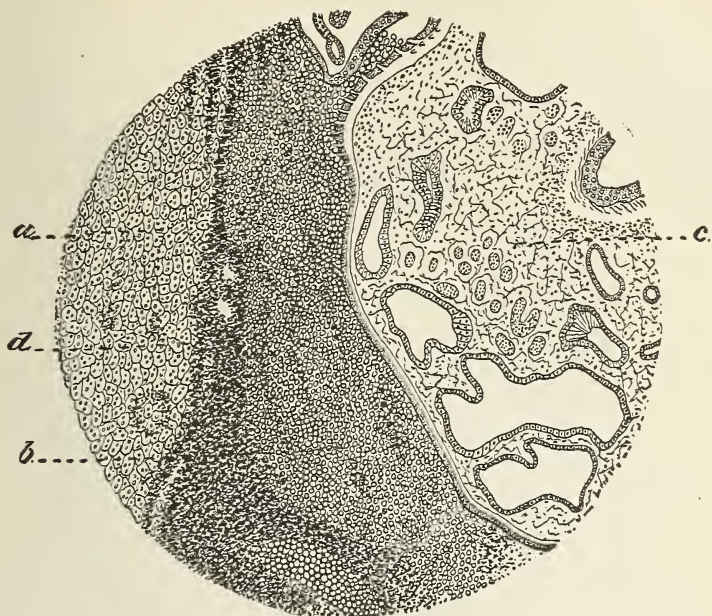


FIG. 31.—Drawing from a microscopic preparation showing a hemorrhage in the parenchyma of the liver caused by the Common Liver Fluke (*Fasciola hepatica*): *a*, atrophic liver tissue; *b*, round cell infiltration; *c*, a portion of the parasite; *d*, hemorrhage. (After Schaper, 1890, Pl. 1, fig. 1.)

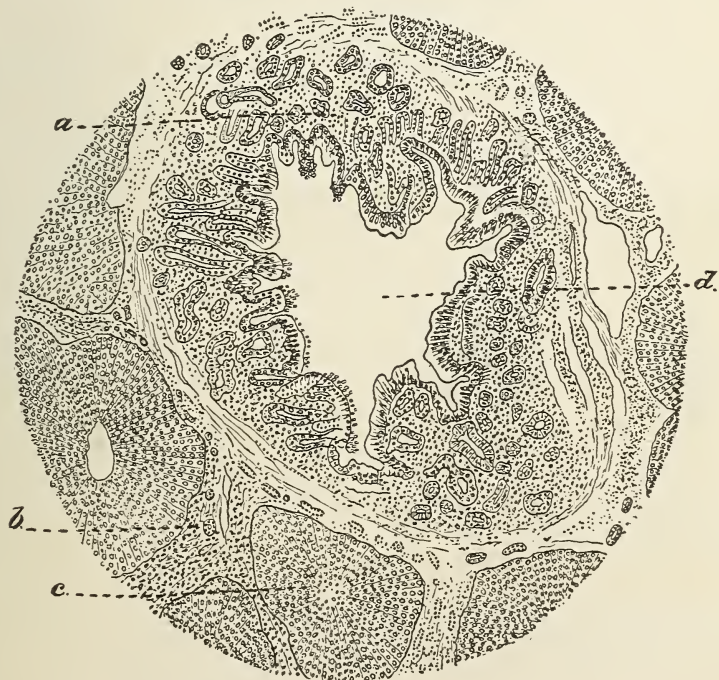


FIG. 32.—Drawing from a microscopic preparation showing the glandular hyperplasia of the mucosa of a gall duct caused by the Common Liver Fluke (*Fasciola hepatica*): *a*, hypertrophied submucosa; *b*, interstitial connective tissue; *c*, compressed lobule; *d*, lumen of the gall duct; thickened fibrous wall of the gall duct. (After Schaper, 1890, Pl. 1, fig. 2.)

Genus DICROCÆLIUM<sup>a</sup> Dujardin, 1845.

GENERIC DIAGNOSIS.—Fasciolidæ: Body of rather slender build, elongate, and flat; anterior and posterior ends more or less pointed. Suckers rather approached to each other; ventral acetabulum usually more highly developed than the oral sucker. Skin smooth. Intestine with pharynx, moderately long esophagus, and long simple ceca.

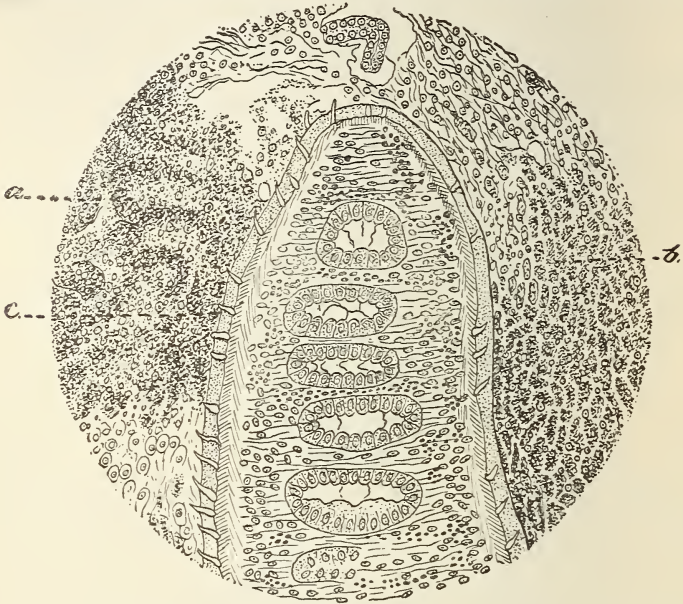


FIG. 33.—Drawing from a microscopic preparation showing a fluke in the tissue of the liver: *a*, necrotic liver tissue; *b*, atrophic liver cells; *c*, spines on the fluke, showing the outline of the body. (After Schaper, 1890, Pl. 3, fig. 5.)

Excretory system simple, tubular. *Genital pore* median, between the suckers. Copulatory organs present, but not highly developed. *Male organs*: Cirrus pouch lies almost entirely anterior of ventral acetabulum; in its posterior end is a more or less coiled vesicula seminalis, anterior of this the moderately developed pars prostatica,

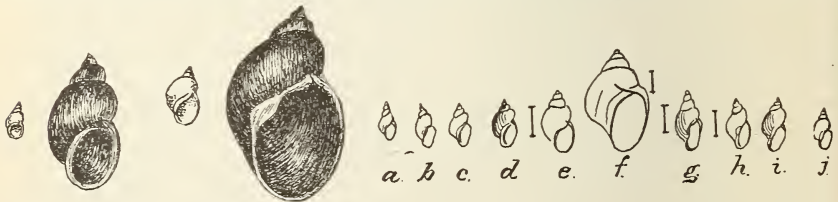


FIG. 34.—*Limnæa truncatula*, natural size and enlarged. (After Leuckart.)

FIG. 35.—*Limnæa peregra*, natural size and enlarged. (After Leuckart.)

FIG. 36.—*Limnæa humilis*, natural size and enlarged. (After Binney.)

and a comparatively long, thin cirrus (including ductus ejaculatorius); testicles compact, one quite straight behind the other, directly posterior of the ventral sucker. *Female organs*: Ovary about median, smaller than the testicles, and immediately

<sup>a</sup>SYNONYMS.—*Distoma* (*Dicrocoelium*) Dujardin, 1845; *Dicrocoelium* Dujardin of E. Blanchard, 1847a; *Dicrocoelium* (misprint) of several authors.



posterior of them, receptaculum seminis and Laurer's canal present; vitellaria moderately developed, lateral of the intestinal ceca; uterine coils numerous, distinctly transverse, confined to space posterior of genital glands. *Eggs* quite numerous;



FIG. 37.—*Linnæa oahuensis*, natural size and enlarged. (After Souleyet.)



FIG. 38.—*Linnæa viator*, natural size and enlarged. (After d'Orbigny.)

when ripe of a more or less deep brown color, and varying in size from 36 to 47  $\mu$  by 21 to 31  $\mu$ .

**HABITAT.**—With one exception, parasitic in liver and gall bladder of warm-blooded animals (mammals and birds).

**TYPE-SPECIES.**—*Dicrocoelium lanceatum* Stiles & Hassall, 1896.

**The Lancet Fluke—DICROCOELIUM LANCEATUM**<sup>a</sup> Stiles & Hassall, 1896—  
of Ruminants, Man, etc.

[Figs. 39 to 41.]

**SPECIFIC DIAGNOSIS.**—*Dicrocoelium*: 4 to 9 mm. long, 2 to 2.4 mm. broad; thin, lanceolate, more pointed anteriorly than posteriorly. Acetabulum slightly larger than oral sucker, the latter slightly subterminal; distance between the two, about one-fifth the length of the body. Skin without spines. Pharynx small (0.25 mm.), globular; esophagus about 2.5 to 3 times as long as the pharynx, so that the bifurcation of the intestine is immediately anterior of the genital pore; intestinal ceca extend to posterior quarter of body. Genital pore about halfway between suckers, immediately posterior of bifurcation of intestine. *Male organs*: Cirrus pouch extends from genital pore to ventral acetabulum and contains the pars prostatica and vesicula seminalis; testicles irregularly lobate, one caudad of the other, directly caudad of ventral acetabulum. *Female organs*: Ovary small, directly caudad of posterior testicle, but anterior of transverse vitelloducts; uterus confined between the intestinal ceca, but in posterior fourth of body there is a tendency for the coils to extend nearer the lateral margins; vitellaria only moderately developed, marginal, in equatorial third of body. *Eggs* 38 to 45  $\mu$  long by 22 to 30  $\mu$  broad, contain embryos when oviposited. Sporocyst, redia, cercaria, and intermediate host undetermined.

**HABITAT.**—Gall ducts of cattle (*Bos taurus*), sheep (*Ovis aries*), ass (*Equus asinus*), man (*Homo sapiens*), etc.

**GEOGRAPHIC DISTRIBUTION.**—Very extended, especially in Europe, but apparently not in England or North America.

<sup>a</sup>**VERNACULAR NAMES.**—English, *Lancet fluke*; German, *der lanzettförmige Leberegel*, *das lanzettförmige Doppelloch*; French, *distome lanceolé*; Italian, *distoma lanceolato*.

**SYNONYMS.**—*Fasciola lanceolata* Rudolphi, 1803 (not Schrank, 1790); *Distoma lanceolatum* (Rudolphi) Mehlis, 1825; "*Distoma (Dicrocoelium) lanceolatum* Mehlis" of Dujardin, 1845; "*Distomum lanceolatum* Mehlis" of Diesing, 1850; "*Dicrocoelium lanceolatum* Dujardin" of Weinland, 1858; "*Fasciola Buchholzi* Jördens, 1801," misprint of Braun, 1889; *Dicrocoelium lanceatum* Stiles & Hassall, 1896.

**BIBLIOGRAPHY.**—No extensive bibliography as yet published. For detailed technical discussion see Leuckart (1889, pp. 359-399). For a review of seven cases of infection compiled for man consult Blanchard, 1888a, pp. 611-612, Leuckart, 1899, pp. 391-399, or Moniez, 1896, pp. 120-122.

Genus OPISTHORCHIS Blanchard,<sup>a</sup> 1895.

GENERIC DIAGNOSIS.—Fasciolidae: Body distinctly, often very greatly, elongated; anterior end attenuated, posterior end broader. Skin smooth, often without spines. Suckers not far separated, and usually not especially large. Intestine with pharynx, short slender esophagus, and long simple ceca. Excretory system with long sigmoid stem usually winding between the testicles, and with short branches. *Genital pore* median, immediately in front of acetabulum. Copulatory organs absent. *Male organs*: Testicles in posterior portion of body, one posterior of the other, more or less distinctly lobate, or even branched. *Female organs*: Ovary simple or lobate, anterior of testicles; Laurer's canal present; receptaculum seminis very greatly developed; uterine coils anterior of testicles and ovary, but not extending materially over the intestinal ceca; vitellaria moderately developed, lateral of intestinal ceca, not extending anteriorly beyond the ventral acetabulum.

HABITAT.—Parasitic in the gall-ducts of warm-blooded animals (mammals and birds).

TYPE SPECIES.—*Opisthorchis felineus* (Rivolta, 1884).

## KEY TO SPECIES OF OPISTHORCHIS REPORTED FOR MAN.

(For species thus far found in the United States, follow Roman type.)

1. Testicles branched, and frequently extending beyond the intestinal ceca into the lateral fields; excretory system runs dorsally of testicles; Asia, but imported cases elsewhere..... *O. sinensis* (p. 35)  
*Testicles may be lobate, but not branched, and are confined to median field between the intestinal ceca; excretory system sigmoid extending between the testicles*..... 2
2. *Spines present on skin; vitellaria extend caudally of first testicle to about the anterior border of posterior testicle; worm not over 12 mm. long; ventral acetabulum close to bifurcation of intestine; India*..... *O. noverca* (p. 33)  
*Spines absent; vitellaria not reaching or barely reaching the first testicle; worm 10 to 18 mm. long; ventral acetabulum some distance from bifurcation of intestine; Europe*..... *O. felineus* (p. 31)

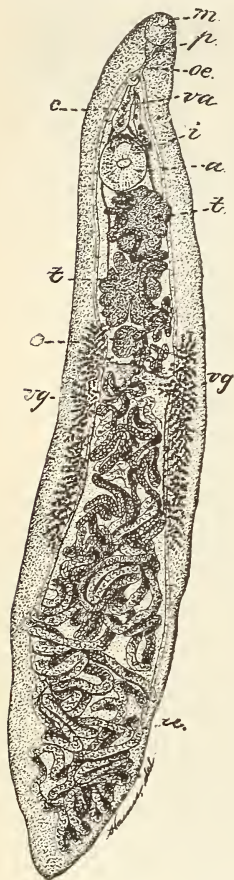


FIG. 39.—Lancet Fluke, enlarged to show the anatomic characters: *ac*, acetabulum; *c. p.*, cirrus pouch; *i*, intestinal ceca; *m*, mouth with oral sucker; *ov.*, ovary; *e*, esophagus; *p. b.*, pharyngeal bulb; *t*, lobate testicles; *ut.*, uterus; *va.*, vagina; *vg.*, vitellogene glands. (After Stiles & Hassall, 1894, Pl. 4, fig. 19.)



FIG. 40.—Egg of Lancet Fluke (*Dicrocoelium lanceatum*), with contained embryo.  $\times 700$ . (After Leuckart, 1889, p. 379, fig. 171.)



FIG. 41.—Free embryo (miracidium) of the Lancet Fluke; *A*, lateral view; *B*, dorsal view. (After Leuckart, 1889, p. 385, fig. 175 *A, B.*)

<sup>a</sup>SYNONYMS.—*Opisthorchis* Blanchard, 1895; *Opistorchis* Railliet, 1896 (misprint); "*Campula* Cobbold," of Stiles & Hassall, 1898 (in part); *Opisthorchie* Stiles, 1901 (misprint).

The European Cat Fluke—*OPISTHORCHIS FELINEUS*<sup>a</sup> (Rivolta, 1884)  
Blanchard 1895—of Cats, Dogs, Man, etc.

[Figs. 42 to 44.]

**SPECIFIC DIAGNOSIS.**—*Opisthorchis*: 8 to 13 mm., seldom 18 mm. long, 1.25 to 2.5 mm. broad; flat, lanceolate, anterior end conical, posterior end rounded; the anterior fifth of the body more or less constricted from the posterior four-fifths; reddish, transparent. Oral sucker and ventral acetabulum of same size, 0.28 mm. in diameter; oral sucker terminal to subterminal; ventral sucker at plane of constriction between anterior fifth and posterior four-fifths of body. Skin without spines. Pharynx small, 0.204 mm. long, 0.161 mm. broad, follows the oral sucker; esophagus 0.2 mm. long; intestinal ceca extend to posterior end of body. *Male organs*: Testicles lobate. *Female organs*: Uterus moderately well developed; ovary slightly lobate; shell gland diffuse, composed of unicellular glands; receptaculum seminis postero-lateral of ovary; vitellaria lateral in equatorial third of body, and composed of seven to nine groups of acini on each side; transverse vitellogene duct runs postero-median. *Eggs* oval, 26 to 30  $\mu$  by 11 to 15  $\mu$ , with sharply defined operculum on the more acute pole; contain ciliated embryo at oviposition. Sporocyst, redia, cercaria, and intermediate host undetermined.

**HABITAT.**—Gall ducts of the domesticated cat (*Felis catus domestica*), domesticated dog (*Canis familiaris*), glutton (*Gulo borealis*), and man (*Homo sapiens*).

**GEOGRAPHIC DISTRIBUTION.**—Europe (Germany, Holland, Italy, France, and Russia).

<sup>a</sup>**SYNONYMS.**—*Distoma conus* Gurlt, 1831 (not Creplin, 1825); "*Distoma lanceolatum*" of von Siebold, 1836 (not *Fasciola lanceolata* Schrank, 1790); "*Distomum lanceolatum* Mehlis" of Diesing, 1850 (sub *D. truncatum*); *Distomum felineum* Rivolta, 1884; "*Distomum conus*" of Sonsino, 1889 (sub *D. truncatum*); *Distomum sibiricum* Winogradoff, 1902; *Distomum (Dicrocoelium) felineum* Rivolta of Braun, 1893; *Distoma (Dicrocoelium) felineum* Rivolta of Stiles, 1894 (sub *D. truncatum*); *Opisthorchis felineus* (Rivolta, 1894) R. Blanchard, 1895; *Opisthorchic felineus* (Rivolta) Stiles, 1901 (misprint).

**BIBLIOGRAPHY.**—Stiles & Hassall, 1894, pp. 426–427.

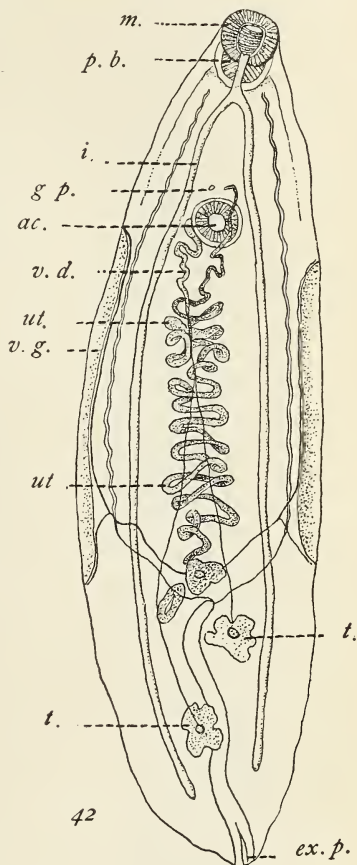


FIG. 42.—Rivolta's (1884) original figure of *Opisthorchis felineus*: *ac.*, acetabulum; *ex. p.*, excretory pore; *g. p.*, genital pore; *i.*, intestinal ceca; *m.*, mouth; *p. b.*, pharyngeal bulb; *t.*, testicles; *ut.*, uterus; *v. d.*, vas deferens; *v. g.*, vitellogene gland.



This parasite has been reported for man in Prussia, and Winogradoff found it in Siberia in 8 (or 9) out of 124 post-mortem examinations of human cadavers. It is essentially an Old World species, but it may be found at any time in Europeans who have immigrated to the United States, and the possibility is by no means excluded that it may be found in American troops who have served in China or the Philippines.

Ward (1895) has recorded this species for cats in Nebraska, but a comparison of his specimens with authentic material of *O. felineus* from Europe has convinced both him and me that the Nebraskan parasite represents a distinct form. Since it is so closely allied to *O. felineus*, further since both species occur in cats and the European form occurs in man also, it need occasion no surprise if Ward's parasite is found sooner or later in man. Its characters may be seen from the following diagnosis:



FIG. 44.—Egg of *Opisthorchis felineus*.  $\times 830$ . (After Braun, 1903, p. 185, fig. 105.)

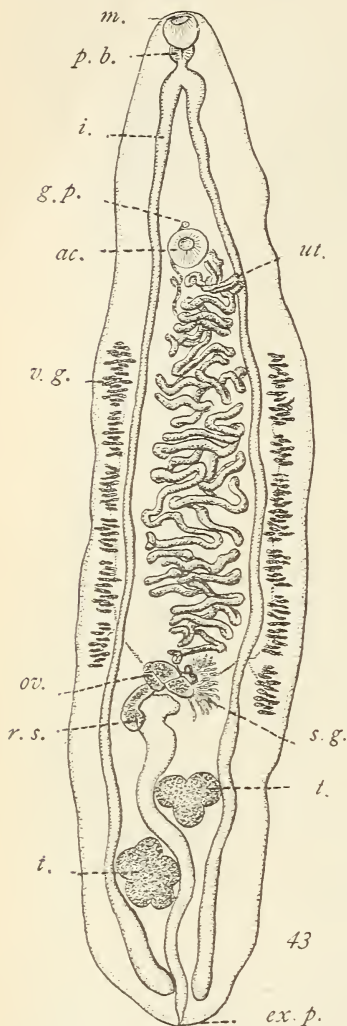


FIG. 43.—*Opisthorchis felineus* from a cat, collected in Prussia by Max Braun. Greatly enlarged to show the anatomy: *ov.*, ovary; *r. s.*, receptaculum seminis; *s. g.*, shell gland; other letters same as fig. 42. (After Stiles & Hassall, 1894, fig. 6.)

postero-lateral of ovary; vitellaria

*Opisthorchis pseudofelineus* <sup>a</sup> Ward, 1901 (fig. 45); *Opisthorchis*: 12 to 20 mm. long, 1 to 2.5 mm. broad; form somewhat similar to that of *O. felineus*, but more elongate. Oral sucker 0.355 mm. by 0.414 mm., terminal to subterminal; ventral acetabulum somewhat smaller, 0.247 mm. by 0.240 mm., situated slightly anterior of border between first and second anterior fourths of body. Skin provided with minute scale-like spines which are lacking, however, on posterior portion of body. Pharynx 0.212 mm. by 0.219 mm.; esophagus 0.175 mm. long; intestinal ceca extend to posterior extremity. *Male organs*: Testicles round or lobate. *Female organs*: Uterus well developed, the coils often being quite crowded; ovary globular; receptaculum seminis large, divided each side into an antovarial portion

<sup>a</sup>SYNONYMS.—“*Distoma felineum*” of Ward, 1895; *Opisthorchis pseudofelineus* Ward, 1901.

BIBLIOGRAPHY.—For more detailed description see Ward, 1895, pp. 152-158.

with about five acini and a post-ovarial portion with two or three acini, each portion provided with its own vitelloduct; the antovarial portion extends from the ovary cephalad to about the boundary between the anterior and equatorial thirds of the body; the postovarial portion extends caudad from the ovary to about the anterior plane of the posterior testicle; Laurer's canal prominent. Eggs 25 to 35  $\mu$  by 12 to 15  $\mu$ . Sporocyst, redia, cercaria, and intermediate host undetermined.

HABITAT.—Gall ducts of the domesticated cat (*Felis catus domestica*) and coyote (*Canis latrans* Say).

GEOGRAPHIC DISTRIBUTION.—United States (Nebraska and Iowa).

Winogradoff reports that in one of his nine cases of *Opisthorchis felineus* in man, he found a small spinose distome, and as *O. felineus* is not spinose, Braun (1896) suggests that the parasite might have been *Metorchis albidus* or *M. truncatus*, species found in cats in Europe.

The Indian Liver-Fluke — OPIS-  
THORCHIS NOVERCA<sup>a</sup> Braun,  
1903—of Man.

[Figs. 46 to 48.]

SPECIFIC DIAGNOSIS. — *Opisthorchis*: 9 to 12.5 mm. long, 2.5 mm. broad; lanceolate more attenuate anteriorly than posteriorly. Oral sucker terminal. Ventral acetabulum much smaller than oral sucker; distance between the two equal to about one-eighth the length of the body, the acetabulum being rather near the bifurcation of the intestine. Skin thickly beset with spines. Pharynx large; esophagus appar-

<sup>a</sup>SYNONYMS.—“*Distoma conjunctum* Cobbold” of Lewis & Cunningham 1872.

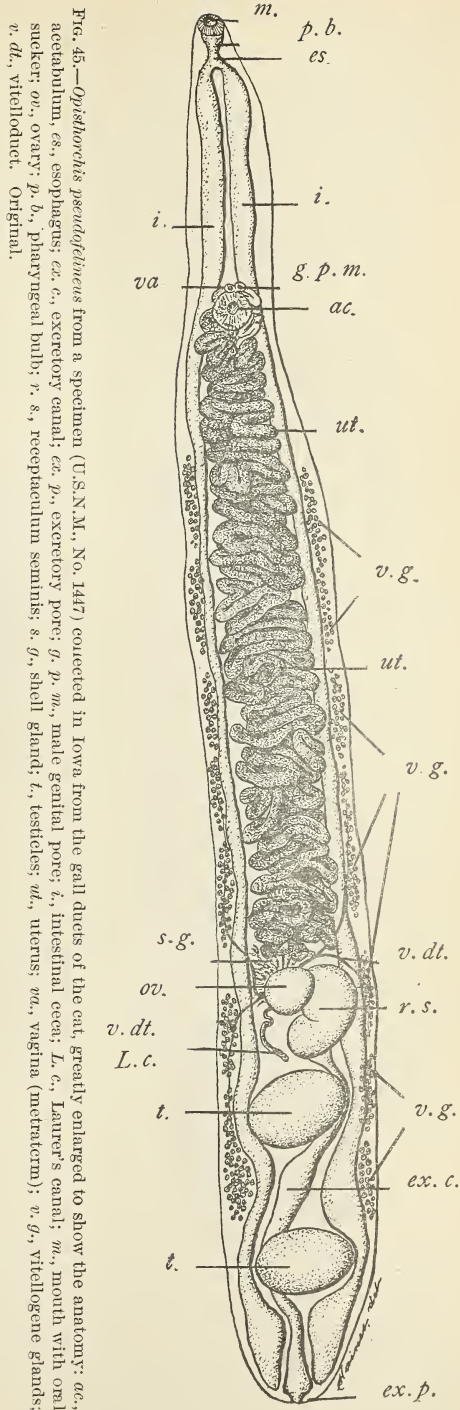


Fig. 45.—*Opisthorchis pseudofelineus* from a specimen (U.S.N.M., No. 1447) collected in Iowa from the gall ducts of the cat, greatly enlarged to show the anatomy: ac., acetabulum, es., esophagus; ex. c., excretory canal; ex. p., excretory pore; g. p. m., male genital pore; i., intestinal caeca; L. c., Laurer's canal; m., mouth with oral sucker; ov., ovary; p. b., pharyngeal bulb; r. s., receptaculum seminis; s. g., shell glands; t., testicles; ut., uterus; va., vagina (metraterm); v. g., vitellogene glands; v. dt., vitelloduct. Original.

ently absent; intestinal ceca extend to about the border of posterior eighth of body. *Male organs*: Testicles apparently round to lobate, situated in posterior third of body. *Female organs*: Uterus apparently poorly developed; ovary?; receptaculum seminis?; Laurer's canal?; vitel-



FIG. 46.—*Opisthorchis noverca*.  
Natural size. (After McConnell, 1876, fig. 2.)

larria apparently extend from ventral acetabulum to posterior testicle. Eggs oval,  $34 \mu$  by  $19$  to  $21 \mu$ . Sporocyst, redia, cercaria, and intermediate host undetermined.

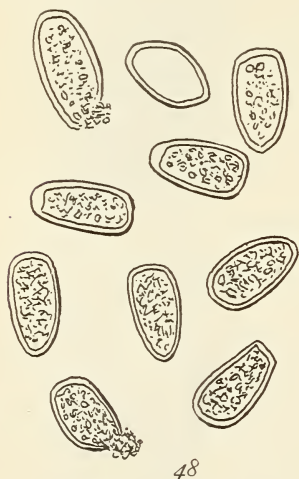


FIG. 48.—Eggs of *Opisthorchis noverca*.  
 $\times 1,300$ . (After McConnell, 1876, fig. 3.)

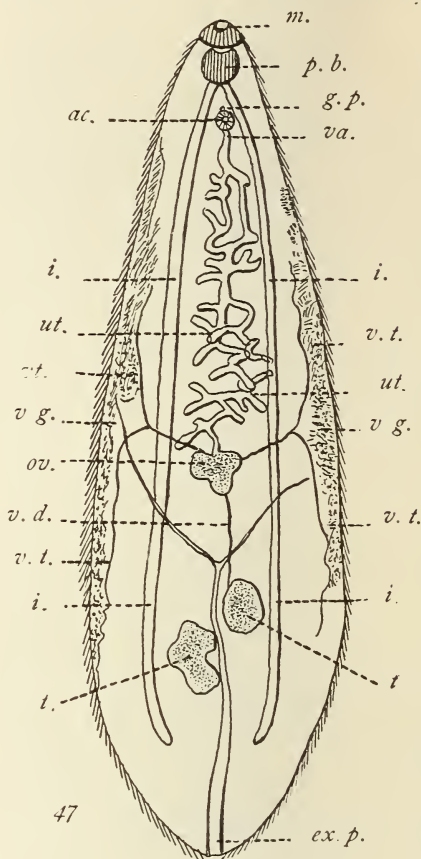


FIG. 47.—Ventral view of *Opisthorchis noverca*, greatly enlarged to show the anatomy: *ac.*, acetabulum; *ex. p.*, excretory pore; *g. p.*, genital pore; *i.*, intestinal ceca; *m.*, mouth with oral sucker; *ov.*, ovary and other adjacent organs; *p. b.*, pharyngeal bulb; *s. g.*, shell gland; *t.*, testicles; *ut.*, uterus; *va.*, vagina; *v. d.*, vas deferens; *v. g.*, vitellaria; *v. t.*, vitello-duct. (After McConnell, 1876, fig. 1.)

HABITAT.—Gall ducts of man (*Homo sapiens*) and pariah dogs (*Canis familiaris*).

GEOGRAPHIC DISTRIBUTION.—India.

This parasite has been confused with *Metorchis conjunctus* (Cobbold, 1862) of the American Red fox (*Canis fulvus*), but the two worms are evidently distinct.

The above diagnosis is based chiefly upon McConnell's figures. The species needs a careful restudy.

For the two cases reported in man, see McConnell, 1876 and 1878.



The Asiatic Liver Fluke—*OPISTHORCHIS SINENSIS*<sup>a</sup> (Cobbold, 1875)  
Blanchard, 1895—of Man.

[Figs. 49 to 62.]



FIG. 49.—The Asiatic liver fluke (*Opisthorchis sinensis*). Natural size, from specimen (U.S.P.H. & M.H.S. No. 9410) collected in San Francisco by Asst. Surg. M. J. White. Original.

SPECIFIC DIAGNOSIS.—

*Opisthorchis*: 10 to 20 mm. long, 2 to 5 mm. broad; flat, lanceolate to oblong oval, attenuate anteriorly, rounded posteriorly; reddish, nearly transparent during life. Oral sucker larger than ventral acetabulum, which is about on border between first and second fourths of body. Skin without spines. Pharynx globular, about 0.22 mm. in diameter; esophagus 0.17 mm. long, not longer than pharynx; bifurcation of intestine nearer to oral

sucker than to acetabulum; intestinal caeca slender, extending to posterior end of body. *Male organs*: Testicles in posterior third of body, branched, usually extending beyond intestinal caeca into the lateral fields and situated ventrally of the sigmoid excretory canal. *Female organs*: Uterus moderately developed; ovary trilobate; immediately anterior of the large elongate vesicula seminalis;

<sup>a</sup> SYNONYMS.—*Distoma sinense* Cobbold, 1875; *Distoma sineuse* of McConnell, 1876 (misprint); *Distomum spathulatum* Leuckart, 1876 (not Creplin, 1849; for *spatulatum* Rudolphi, 1819); *Distomum spatulatum* Cobbold, 1879 (not Rudolphi, 1819); *Distoma hepatis endemicum* Baelz, 1883; *Distoma hepatis innocuum* Baelz, 1883; *Distoma hepatis perniciosum* Baelz, 1883; *Distoma spatulatum* (Cobbold, 1879) Blanchard, 1888; *Distoma japonicum* R. Blanchard, 1886 or 1888; *Distomum sinense* (Cobbold) Leuckart, 1889; *Opisthorchis sinensis* (Cobbold, 1875) R. Blanchard, 1895; *Dicrocalium sinense* (Cobbold) Moniez, 1896.

BIBLIOGRAPHY.—For technical zoological discussion, see Leuckart (1889, pp. 336 to 355, figs. 154 to 161); for medical discussion, with record of 76 autopsies, see Katsurada (1900, pp. 479–504). White (1902, p. 523) has found 18 cases in San Francisco.

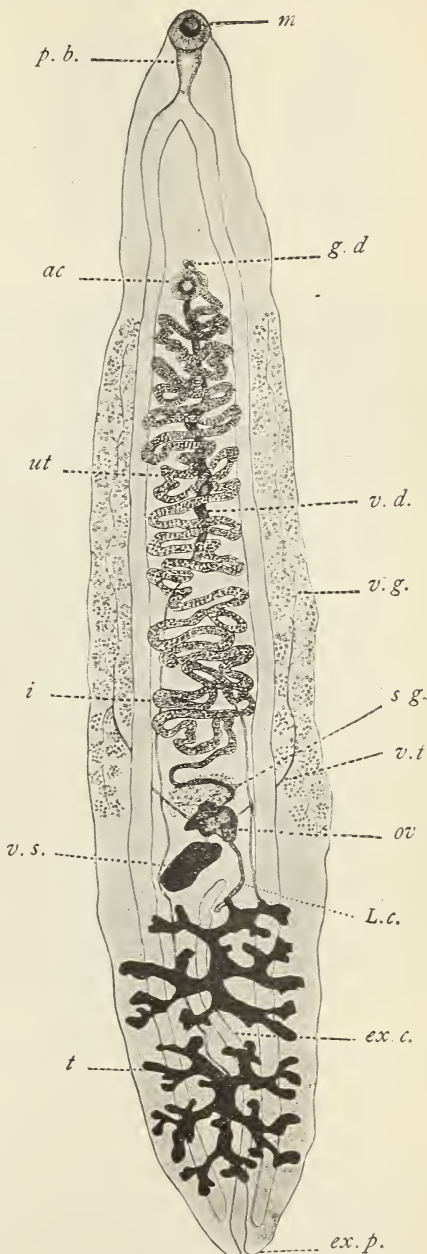
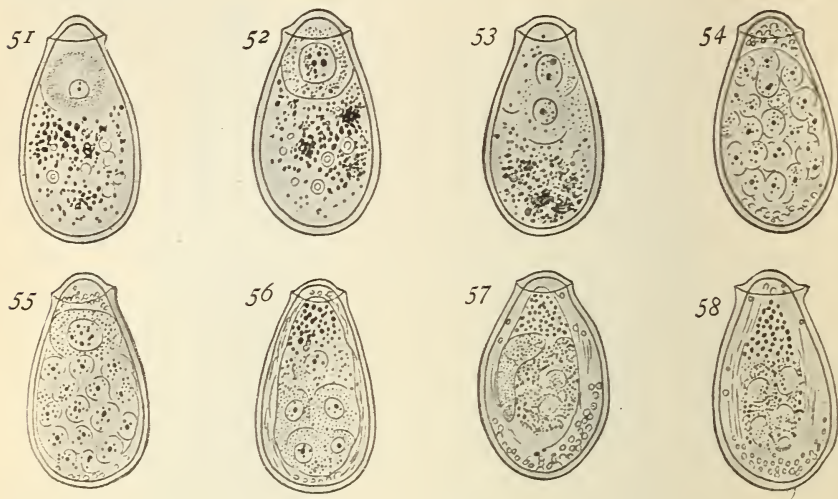


FIG. 50.—The same, ventral view, greatly enlarged to show the anatomy: *ac.*, acetabulum; *ex. c.*, excretory canal; *ex. p.*, excretory pore; *g. p.*, genital pore; *i.*, intestinal caeca; *L. c.*, Laurer's canal; *m.*, mouth, with oral sucker; *or.*, ovary; *p. b.*, pharyngeal bulb; *s. g.*, shell gland; *t.*, testicles; *ut.*, uterus; *v. d.*, vas deferens; *v. g.*, vitellogene glands; *v. s.*, vesicula seminalis; *v. t.*, vitellocyst. Original.

vitellaria moderately developed, occupying about the equatorial third of the body. Eggs oval, 27 to 30  $\mu$  by 15 to 17  $\mu$ ; dark brown, with sharply defined operculum; contain ciliated embryo at oviposition. Sporocyst, redia, cercaria, and intermediate host undetermined.

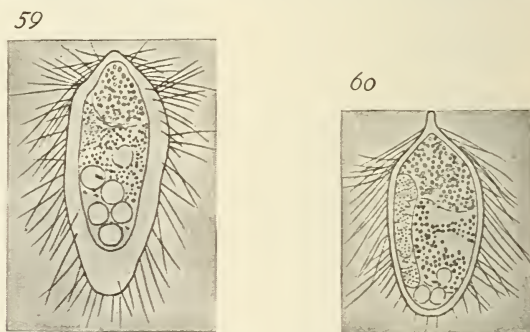


FIGS. 51-58.—Eggs of *Opisthorchis sinensis* in different stages of development, as found in the uterus. Note the operculum at one end. Greatly enlarged. (After Katsurada, 1900, pl. 13, figs. 2-9.)

HABITAT.—Gall ducts, pancreatic ducts, duodenum, and stomach of man (*Homo sapiens*) and cats (*Felis catus domestica*).

GEOGRAPHIC DISTRIBUTION.—Asia; sporadic imported cases elsewhere.

Several imported cases of this parasite have been found in the United States and Canada. In some of the Japanese cases that have



FIGS. 59-60.—Free embryos (miracidia) of same. Greatly enlarged. (After Katsurada, 1900, pl. 13, figs. 10-11.)

been recorded several thousand parasites have been present, and while the hepatic ducts are more frequently affected, some cases are recorded of the presence of this fluke in the pancreatic ducts, in the duodenum, and in the stomach. See p. 8.



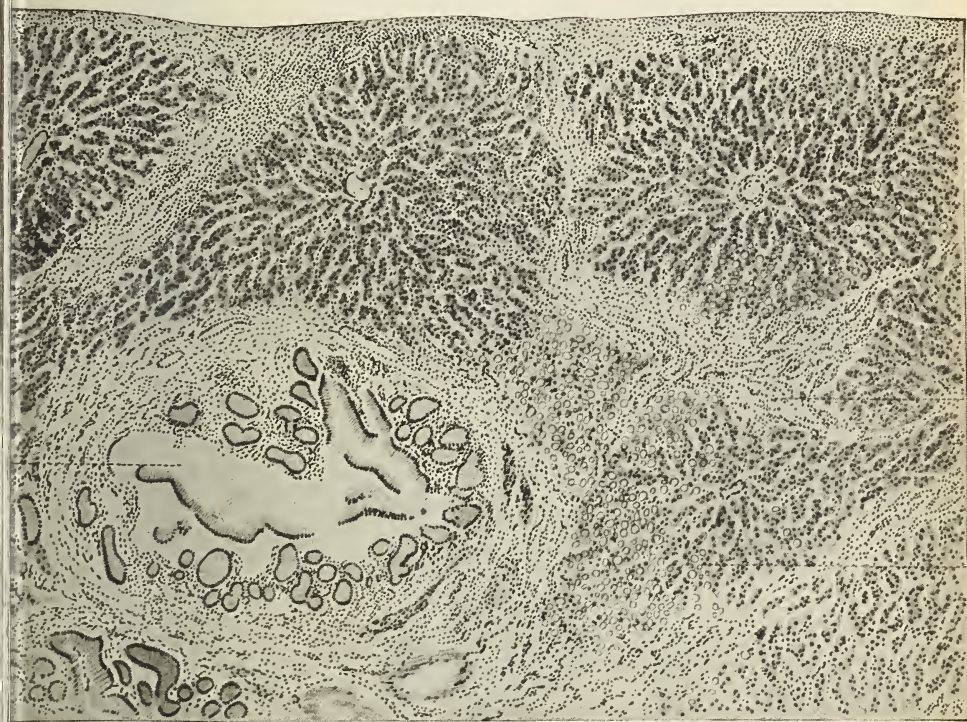


Fig. 61.—Section through the left lobe of the liver, showing lesions caused by *Opisthorchis sinensis*: *a.*, thickened gall duct; *b.*, hyperplastic connective tissue; *c.*, thickened capsule; *d.*, fatty or more or less atrophied liver tissue.  $\times 40$ . (After Katsurada, 1900, pl. 13, fig. 12.)

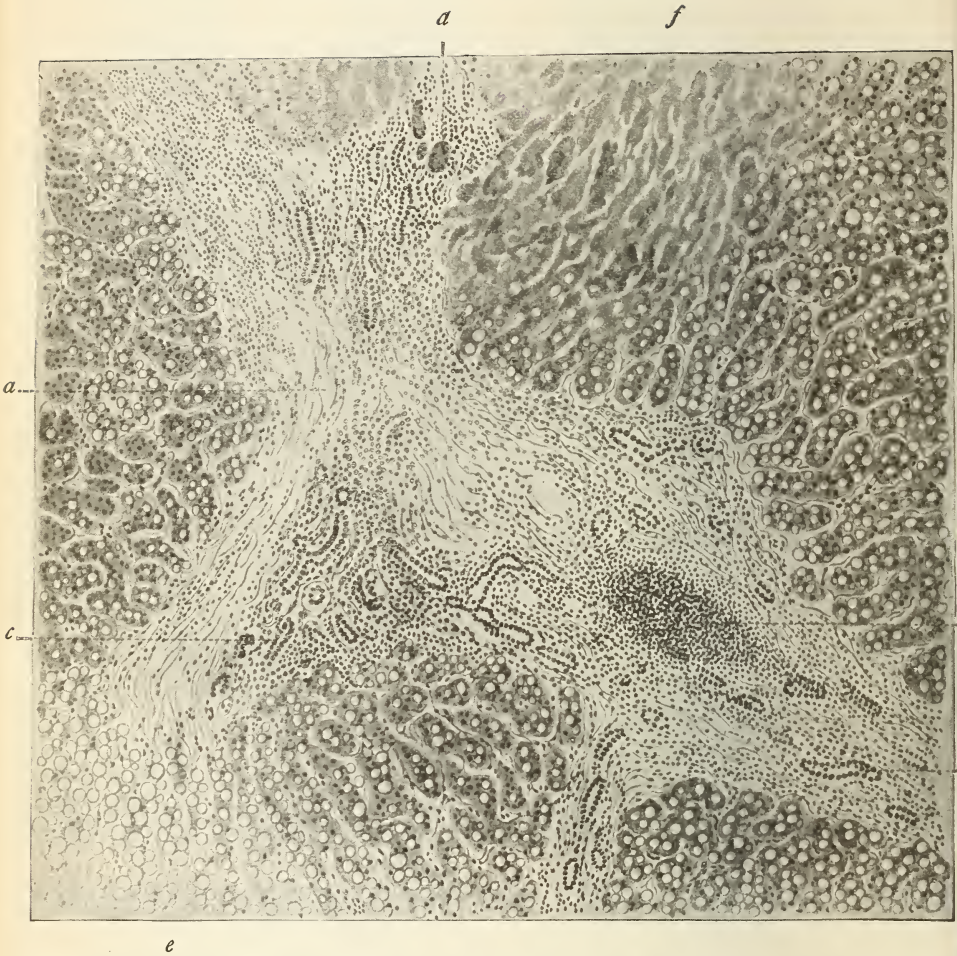


FIG. 62.—Section through the right lobe of the liver, showing lesions caused by *Opisthorchis sinensis*: *a*, hyperplastic connective tissue; *b*, small cell infiltration; *c*, newly formed gall ducts; *d*, small interacinous gall duct filled with gall; *e*, fatty degenerated liver tissue; *f*, necrotic liver tissue.  $\times 40$ . (After Katsurada, 1900, pl. 13, fig. 13.)



## INTESTINAL DISTOMATOSIS.

The exact extent to which distomes in the intestine incommode a patient is not yet determined. It seems rather doubtful whether *Heterophyes* is of much appreciable medical importance, although a heavy infection should not be ignored. *Fasciolopsis*, being much larger, is probably of more importance. Cobbold, for instance, records it for two cases where there were signs of intestinal irritation, such as repeated attacks of diarrhea. The medical importance of *Gastrodiscus* is yet to be established.

In general, it may be said that the importance of intestinal as well as other flukes is a relative question. A few parasites may do little harm, still they actually must do some injury, even if it amounts to simply taking food which should go to the host; an increased infection increases the amount of damage.

CLINICAL DIAGNOSIS.—Microscopic examination of fresh stools for eggs; examine also the sputum and the urine in order to eliminate the lung infection with *Paragonimus* and the blood infection with *Schistosoma*.

SYMPTOMS.—Still to be further determined: probably general symptoms of intestinal irritation. Indigestion, nausea, headache, diarrhea, and bloody stools have been observed.

TREATMENT.—Favorable results have been obtained by Dobson with thymol. Aloes, followed by castor oil, also aloes and asafetida, followed by scammony, have failed (Cobbold's cases). As the parasites are plathelminthes, I would suggest the use of same anthelmintics adopted for tapeworms.



FIG. 63.—*Fasciolopsis buskii*. Natural size. (After Leuckart, 1863, p. 586, fig. 196.)

### Family FASCIOLIDÆ.

Genus FASCIOLOPSIS Looss,<sup>a</sup> 1899.

GENERIC DIAGNOSIS.—Fasciolidæ: Body rather large, flat, about one-third as broad as long, lanceolate to tongue-shaped. Cephalic cone wanting. Skin without spines. Ventral acetabulum larger than oral sucker and nearer anterior end. Intestine with short prepharynx, strong globular pharynx, and exceedingly short esophagus; intes-

<sup>a</sup> SYNONYMS.—*Fasciolopsis* Looss, 1899; *Fasciolopsis* Odhner, 1902 (misprint).

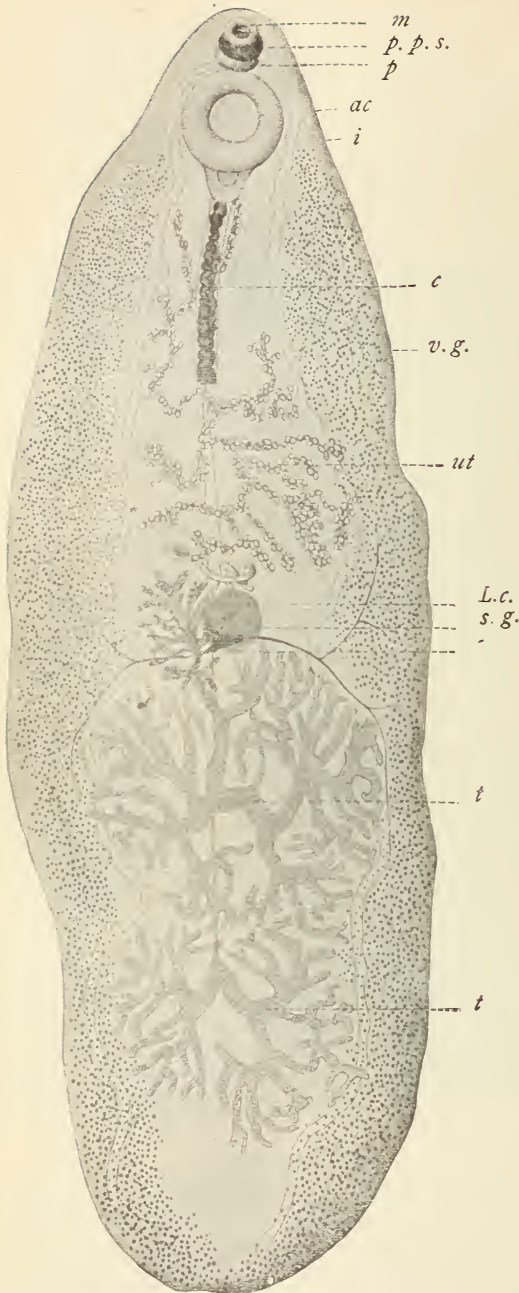


FIG. 64.—Ventral view of *Fasciolopsis buskii*, enlarged to show the anatomy: *ac.*, acetabulum; *c.*, cirrus; *L.c.*, Laurer's canal; *m.*, mouth with oral sucker; *or.*, ovary; *p.*, pharynx; *p. p. s.*, prepharyngeal sphincter; *s.g.*, shell gland; *t.*, testicles; *ut.*, uterus; *v.g.*, vitellogene glands.  $\times 6$ . (After Odhner, 1902, fig. 1.)

tinal ceca branch immediately anterior of ventral acetabulum, are narrow and long, extending along inner margin of vitellaria to the posterior end of the body, and are not provided with secondary branches. Excretory system similar to that of *Fasciola*. *Genital pores* empty into genital sinus which is situated in the ventro-median line immediately anterior of acetabulum. Copulatory organs present, the cirrus pouch being a long, straight, median tube extending caudad to a point about half way between ventral acetabulum and shell-gland. *Male organs*: Testicles in the posterior half of median field, side by side, or one posterior of the other, both branched dicotomously. *Female organs*: Ovary moderately developed, branched, located at equator, right of median line; receptaculum seminis absent; Laurer's canal present; vitellaria well developed, with very small acini, and extend from plane of ventral acetabulum to caudal pole of body, where the acini from the two sides may meet in the median line; transverse section of body shows acini to be superficial both dorsally and ventrally; transverse vitello-ducts meet in median line of equator to form the vitelline reservoir; shell-gland compact, well developed, globular; uterus extends from equator forward, with lateral coils, and leads to the well-developed metraterm at caudal border of acetabulum. *Eggs* rather numerous, similar in form to those of *Fasciola*.

**HABITAT.**—Intestine of mammals.

**TYPE SPECIES.**—*Fasciolopsis buskii* (Lankester, 1857).

Busk's Intestinal Fluke—*FASCIOLOPSIS BUSKII*<sup>a</sup> (Lankester, 1857) Stiles, 1901—of Man.

[Figs. 63 to 66.]

SPECIFIC DIAGNOSIS.—*Fasciolopsis*: 24 to 37 mm. (75 mm. after Busk) long, 5.5 to

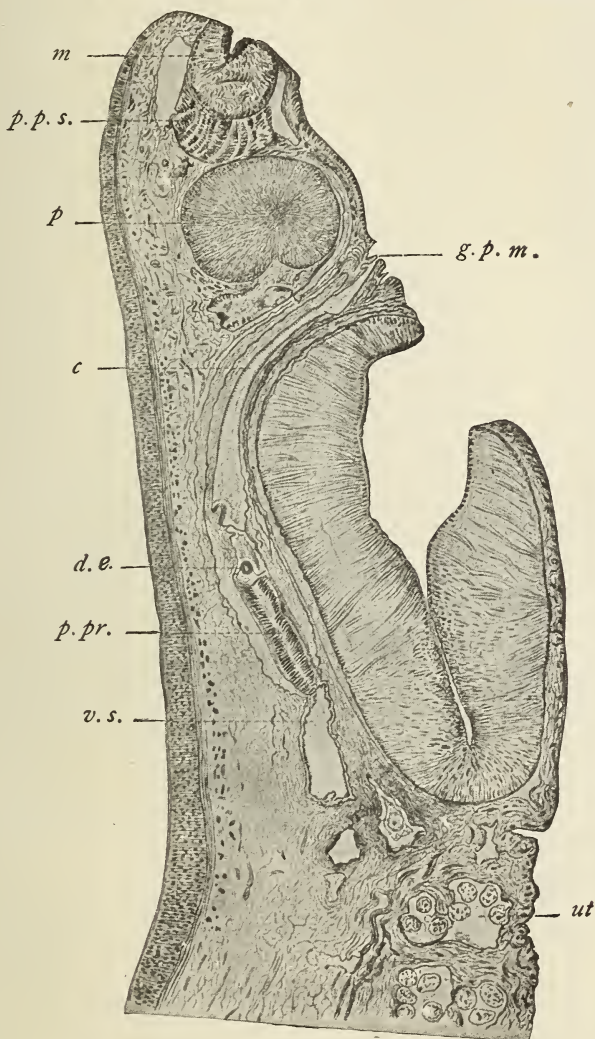


FIG. 65.—Sagittal section of cephalic end of *Fasciolopsis buskii*, slightly to the right of the median line: *d. e.*, ductus ejaculatorius; *g. p. m.*, male genital pore; *p. pr.*, pars prostatica; *v. s.*, vesicula seminalis; other letters same as in fig. 64.  $\times 35$ . (After Odhner, 1902, fig. 2.)

12 or 14 mm. broad, 1.5 to 2 mm. thick; maximal breadth in equatorial portion;

<sup>a</sup>SYNONYMS.—*Distoma buskii* Lankester, 1857; *Dicrocoelium buskii* (Lankester) Weinland, 1858; *Distoma crassum* Cobbold, 1860 (not von Siebold, 1837); *Distomum crassum* (Cobbold) Leuckart, 1863; "*Distomum hepaticum*" of Leidy, 1873, p. 364; *Distoma buski* Blanchard, 1888; *Dicrocoelium buski* Blanchard 1888; "*Distoma (Dicrocoelium) buski*" of Railliet, 1893; *Distomum buski* (Blanchard) Braun, 1895; *Distoma granum* Huber, 1896 (misprint); *Fasciolopsis buskii* (Lankester) Stiles, 1901; *Fasciolopsis buski* (Blanchard) Odhner, 1902; *Fasciolopsis buski* (Blanchard) Odhner, 1902.

BIBLIOGRAPHY.—Cobbold, 1879, pp. 20-29. For more recent technical discussion with historical review, see Odhner, 1902, pp. 573-581.



more attenuate anteriorly than posteriorly, ventral surface flat, dorsal surface slightly convex, margins very thin. Oral sucker ventro-subterminal, small, 0.5 mm. in diameter, 0.33 mm. deep. Ventral acetabulum 1.6 to 2 mm. in diameter, but elongated caudally directly under the ventral surface in a 2 to 8 mm. long sack; center of acetabulum 1.8 to 2 mm. from anterior end of body. Skin without spines. Prepharynx 0.28 mm. long; pharynx 0.7 mm.; esophagus very short so that the bifurcation of the intestine occurs about on anterior plane of acetabulum; ceca with two characteristic curves toward median line, one at equator, the other between the testicles. *Male organs*.—Cirrus pouch cylindrical, median, nearly one-fourth as long as the body, 0.25 to 0.33 mm. thick, straight, extending from genital pore to about midway to shell gland (equator); it contains a long sinuous vesicula seminalis with a long blind sack possessing lateral branches, this sack reaching from a short distance caudad of acetabulum to about 0.5 mm. from caudal end of pouch; pars prostatica 0.5 mm. long, ductus ejaculatorius rather short, provided with fine spines; vasa deferentia near median line; testicles one posterior of the other; branches of posterior testicle extend to within about 3 mm. of the caudal end of the body. *Female organs*: Vitelline reservoir rather small; shell gland 1 to 1.5 mm. in diameter. *Eggs* numerous, 120 to 130  $\mu$  long by 77 to 80  $\mu$  broad. Sporocyst, redia, cercaria, and intermediate host undetermined.

*HABITAT*.—Small intestine of man (*Homo sapiens*); Asia.

This parasite has been reported several times for man, all the cases being of Asiatic origin. Judging from the writings of Dobson (1893a, 1893b) and Giles (1892, 1893) this parasite is probably more common, especially in India, than is generally supposed.

Rathouis's Intestinal Fluke—*FASCIOLOPSIS RATHOUISEI* <sup>a</sup> (Poirier, 1887) Ward, 1903.

[Fig. 67.]

*SPECIFIC DIAGNOSIS*.—*Fasciolopsis*: 25 mm. long, 16 mm. broad; whitish, tinted with brown on the margins; oblong oval, obtuse, anterior end appears to be provided with a more or less distinct short cephalic cone, 3 to 5 mm. broad. Oral sucker (?) subterminal, very small, its opening not over 0.5 mm. in diameter (after Moniez), or 1.5 mm. (after Braun). Ventral acetabulum much larger, situated about 2 mm. from the oral sucker, its circular orifice 2 mm. in diameter. Skin without spines. Prepharynx (?); pharynx (?); esophagus (?); intestinal ceca (?). *Male organs*: Cirrus pouch (?) (apparently long); vasa deferentia apparently rather divergent; testicles side by side. *Female organs*: Ovary caudad of transverse

FIG. 66.—Dorsal view of that portion of the cirrus pouch which lies caudally of the acetabulum: *ac.*, acetabulum; *c. v. s.*, cul-de-sac of the vesicula seminalis; *v. d.*, vas deferens; *v. s.*, vesicula seminalis. (After Odhner, 1902, fig. 3.)

<sup>a</sup> *SYNONYMS*.—*Distomum rathouisi* Poirier, 1887; *Distoma rathonisii* Huber, 1894 (misprint); *Fasciolopsis rathouisi* (Poirier) Ward, 1903.

vitello-duct. Eggs ovoid,  $150\ \mu$  long by  $80\ \mu$  broad. Sporocyst, redia, cercaria, and intermediate host undetermined.

HABITAT.—Intestine or (?) gall ducts of man (*Homo sapiens*); Asia.

The original description by Poirier (1887) is not accessible to me. Most authors consider this species identical with *Fasciolopsis buskii*, but Moniez (1896) has questioned their identity and Odhner's (1902) recent work seems to prove that the two forms are distinct.

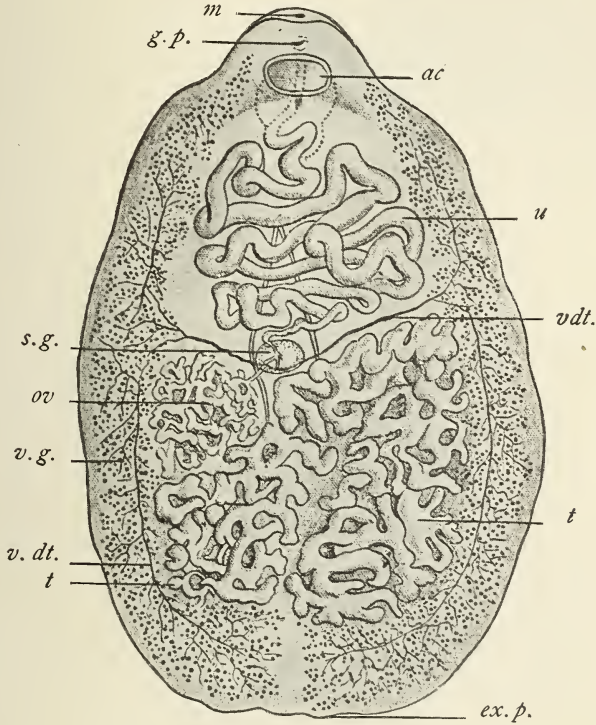


FIG. 67.—Ventral view of *Fasciolopsis rathouisi*, enlarged to show the anatomy: *ac.*, acetabulum; *ex. p.*, excretory pore; *g. p.*, genital pore; *m.*, mouth with oral sucker; *ov.*, ovary; *s. g.*, shell gland; *t.*, testicle; *u.*, uterus; *v. g.*, vitellogene gland; *vdt.*, vitello-duct. (After Poirier, 1887 [from Railliet, 1893, p. 363, fig. 243].)

### Genus HETEROPHYES<sup>a</sup> Cobbold, 1866.

GENERIC DIAGNOSIS.—Fasciolidae: <sup>b</sup> Body small, contractile neck not very sharply defined from body; anterior end more contractile; posterior end more or less bluntly rounded, plump, and less motile. Skin thickly beset with scale-like spines, except for a small area at aboral pole. Oral sucker without thorns; ventral acetabulum situated at the border between the anterior more contractile, and aboral plumper, less contractile portion of body, and is considerably larger than oral sucker. Intes-

<sup>a</sup>SYNONYMS.—*Heterophyes* Cobbold, 1866 (probably earlier); *Cotylogonimus* Lühe, 1899; *Cænogonimus* Looss, 1899.

<sup>b</sup>This generic diagnosis includes some characters which in reality belong to the diagnosis of the subfamily.

tine with pharynx closely following the oral sucker; esophagus moderately long; intestinal ceca simple, extending to extreme aboral end of body. *Genital pore* posterolateral of and in immediate vicinity of ventral acetabulum; it is surrounded by a muscular ring (*genital ring*), the outer free margin of which is provided with a not quite complete wreath of bent chitinous rods with lateral branches. True copulatory organs absent; male and female genital tubes unite before reaching the pore, thus forming a genital cloaca. *Male organs*: Testicles oval, in extreme aboral end of body, on same transverse plane, their longitudinal axis nearly at right angles to the longi-

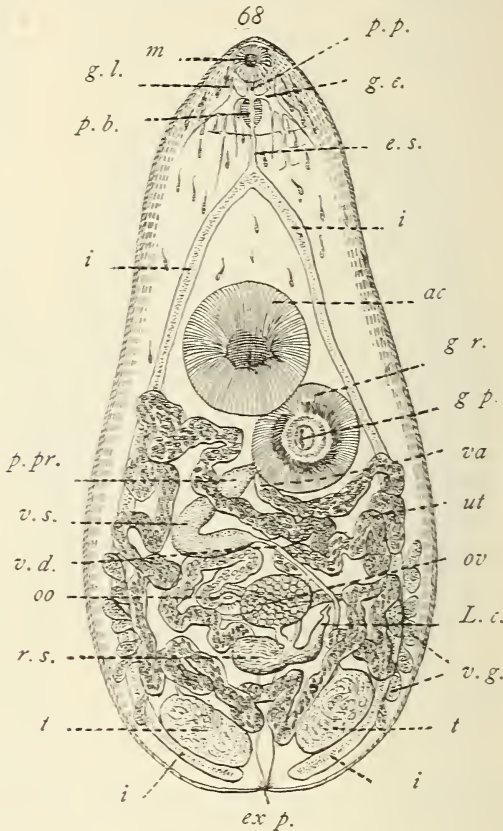


FIG. 68.—Ventral view of *Heterophyes heterophyes*, enlarged to show the anatomy: *ac.*, acetabulum; *es.*, esophagus; *ex. p.*, excretory pore; *g. c.*, cerebral ganglion; *gl.*, glands; *g. p.*, genital pore; *g. r.*, genital ring; *i.*, intestinal ceca; *L. c.*, Laurer's canal; *m.*, mouth with oral sucker; *oo.*, ootyp; *ov.*, ovary; *p. b.*, pharyngeal bulb; *p. p.*, prepharynx; *p. pr.*, pars prostatica; *r. s.*, receptaculum seminis; *t.*, testicle; *ut.*, uterus; *va.*, vagina (metraterm); *v. d.*, vas deferens; *v. g.*, vitellogene glands; *v. s.*, vesicula seminalis; *v. t.*, vitellooduct. [After Looss, 1894, fig. 1.]

tudinal axis of the body; vesicula seminalis flexed, anterior end of latter forming a pars prostatica, both lying free in the parenchyma. *Female organs*: Ovary globular, median, or lateral, anterior of testicles; receptaculum seminis as large as ovary and building a sac-like evagination of Laurer's canal; vitellaria but slightly developed, situated on the margins of the posterior division of the body. Uterine coils not numerous; they extend laterally nearly to the aboral end, never posterior of the testicles, and not anterior of the ventral acetabulum. *Eggs* not numerous, with dark colored thick shell, 20 to 30  $\mu$  by 10 to 17  $\mu$ .

HABITAT.—Intestine of mammals and birds.

TYPE SPECIES.—*Heterophyes heterophyes* (Siebold, 1853) Stiles, 1901.



The Egyptian Intestinal Fluke—**HETEROPHYES HETEROPHYES**<sup>a</sup> (Siebold, 1852), Stiles, 1901—of Man, Dogs, and Cats.

[Figs. 68 to 71.]

**SPECIFIC DIAGNOSIS.**—*Heterophyes*: 1 to 1.7 mm. long, 0.3 to 0.7 mm. broad; reddish, elongate, oval. Scales quadrate, 5 to 6  $\mu$  long by 4  $\mu$  broad; distal margin serrate with 6 to 9 points. Oral sucker 0.09 mm. in diameter, terminal to subterminal, about one-third as large as ventral acetabulum (0.23 mm.), which is in about the middle of the body; genital ring 0.15 mm. Prepharynx short, may attain 80  $\mu$  in length; pharynx 50 to 70  $\mu$  long, 40 to 50  $\mu$  in diameter; esophagus extends to a point about midway between the oral pole and the center of the acetabulum. Intestinal ceca thin, extending posteriorly and ending at the excretory bladder. The lateral ends of the vitellaria extend beyond the intestinal ceca, and some follicles extend ventrally. *Eggs* light brown, thick-shelled, oval, 20 to 30  $\mu$  by 15 to 17  $\mu$ ,

contain ciliated embryo when oviposited. Sporocyst, redia, cercaria, and intermediate host undetermined.

**HABITAT.**—Small intestine of man (*Homo sapiens*), dogs (*Canis familiaris*), cats (*Felis domestica*), and (?) fox (—).

**GEOGRAPHIC DISTRIBUTION.**—Egypt, Japan.



FIG. 70.—Chitinous rods of genital ring.  $\times 700$ . (After Looss, 1894, pl. 1, fig. 5.)

**Family PARAMPHISTOMIDÆ.**  
**Genus GASTRODISCUS** Leuckart, 1877.

**GENERIC DIAGNOSIS.**—Paramphistomidæ, Cladorchinæ (Ventral acetabulum at posterior end. Two pharyngeal pockets present, testicles branched, vas deferens without pars maculosa, cirrus pouch present): Body divided into an anterior rather slender conical portion, and a posterior flattened ventrally concave disk, acetabulum small, ventral.

**TYPE SPECIES.**—*Gastrodiscus polymastos* Leuckart, 1877.

According to the recent revision of the amphistomes published by Fischøder (1902), the amphistome reported for man belongs to the genus *Gastrodiscus*. Stages of the life cycle of the Conical Amphistome (*Paramphistomum cervi*) are here introduced (figs. 79 to 83) to illustrate the biology of this group.

<sup>a</sup> **SYNONYMS.**—*Distomum heterophyes* von Siebold, 1852; *Dicrocælium heterophyes* (Siebold) Weinland, 1858; *Distoma heterophyes* (Siebold) Cobbold, 1860; *Heterophyes ægyptiaca* Cobbold, 1866 (probably earlier); *Mesogonimus heterophyes* (Siebold) Raillet, 1890; *Cænogonimus heterophyes* (Siebold) Looss, 1899; *Cotylogonimus heterophyes* (Siebold) Braun, 1901.

**BIBLIOGRAPHY.**—For detailed anatomical discussion see Looss (1894, pp. 1-42, pl. 1, figs. 1-8; pl. 2, figs. 9-12).

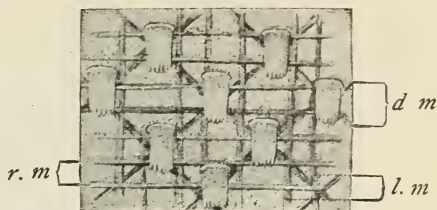


FIG. 69.—A portion of the skin, showing the peculiar quadrate spines, the (*dm.*) diagonal muscles, the (*lm.*) longitudinal muscles, and the (*rm.*) ring or circular muscles.  $\times 1060$ . (After Looss, 1894, pl. 2, fig. 9.)



FIG. 71.—Mature egg of *Heterophyes heterophyes*, containing the fully developed embryo. Note the operculum at one pole.  $\times 700$ . (After Looss, 1894, pl. 2, fig. 12.)

The Asiatic Amphistome—*GASTRODISCUS HOMINIS*<sup>a</sup> (Lewis & McConnell, 1876) Fischæder, 1901—of Man.

[Figs. 72 to 78.]

SPECIFIC DIAGNOSIS.—*Gastrodiscus*: 5 to 8 mm. long, 3 to 4 mm. broad; reddish in color (fresh specimen). *Genital pore* about in middle of the anterior portion at



FIG. 72.—A portion of human intestine slit open, with specimens of *Gastrodiscus hominis*. Natural size. (After Lewis & McConnell, 1876, pl. 3, fig. 1.)

bifurcation of the intestine. Testicles 2, lobate; vas deferens very sinuous. Disk without papillæ. Eggs oval,  $150\ \mu$  by  $72\ \mu$  with operculum.

HABITAT.—Cecum and colon of man (*Homo sapiens*).

GEOGRAPHIC DISTRIBUTION.—Asia.

<sup>a</sup>SYNONYMS.—*Amphistoma hominis* Lewis & McConnell, 1876; *Amphistomum hominis* (Lewis & McConnell) Davaine, 1877; *Gastrodiscus hominis* (Lewis & McConnell) Fischæder, 1901.

BIBLIOGRAPHY.—For the cases thus far reported see Lewis & McConnell (1876, pp. 182–186), Dobson (1893a, 1893b), and Giles (1892, 1893). Judging from the writings of Dobson and Giles, this parasite seems to be much more common in India than is generally supposed.



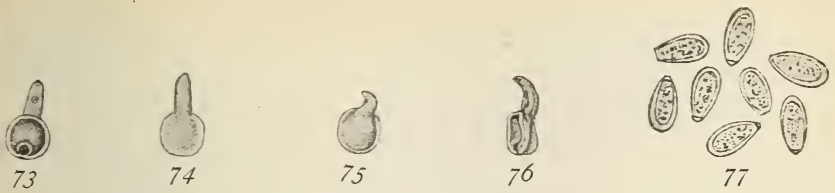


FIG. 73.—Ventral view of *Gastrodiscus hominis*, showing oral sucker, genital pore, sucking disk, and acetabulum.  $\times 2$ . (After Lewis & McConnell, 1876, pl. 3, fig. 2a.)

FIG. 74.—Dorsal view of same.  $\times 2$ . (After Lewis & McConnell, 1876, pl. 3, fig. 2b.)

FIG. 75.—The same.  $\times 2$ . (After Lewis & McConnell, 1876, pl. 3, fig. 2c.)

FIG. 76.—Lateral view of same.  $\times 2$ . (After Lewis & McConnell, 1876, pl. 3, fig. 2d.)

FIG. 77.—Eggs of *Gastrodiscus hominis*.  $\times 65$ . (After Lewis & McConnell, 1876, pl. 3.)

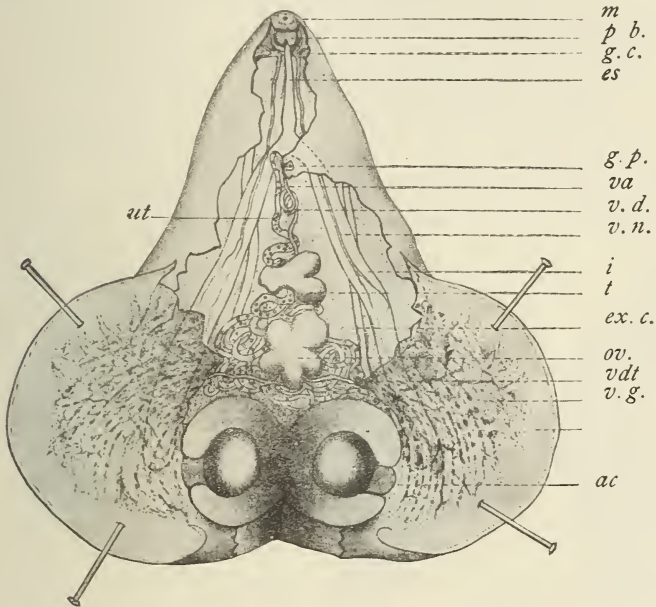


FIG. 78.—*Gastrodiscus hominis*, partially dissected to show the anatomy: *ac.*, acetabulum; *es.*, esophagus; *ex. c.*, excretory canal; *g. c.*, cerebral ganglion; *g. p.*, genital pore; *i.*, intestinal caeca; *m.*, mouth with oral sucker; *ov.*, ovary; *p. b.*, pharyngeal bulb; *t.*, testicle; *ut.*, uterus, with eggs; *va.*, vagina (metraterm); *v. d.*, vas deferens; *v. dt.*, vitellogenic duct; *v. g.*, vitellogene gland; *v. n.*, ventral nerve.  $\times 12$ . (After Lewis & McConnell, 1876, p. 185.)

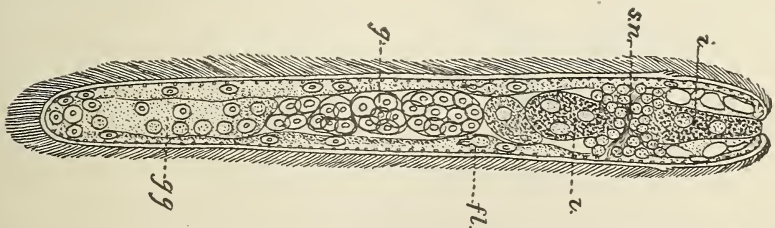


FIG. 79.—Dorsal view of the free embryo (miracidium) of the Conical Amphistome (*Paramphistomum cervi*) about to enter the intermediate host; *fl.*, end portion of excretory system; *g.*, germ cells; *gg.*, matrix of germ cells; *i.*, rudimentary intestine; *sn.*, nervous system.  $\times 285$ . (After Looss, 1896, pl. 12, fig. 125.)

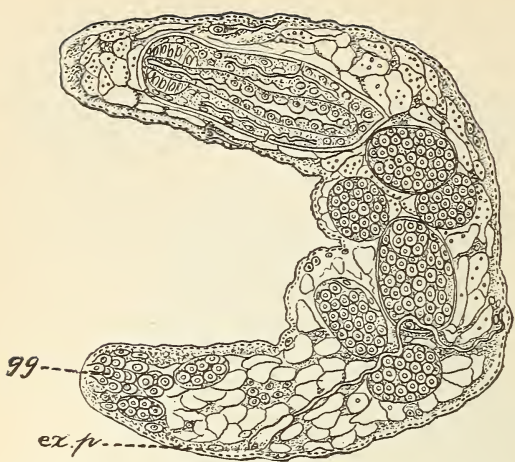


FIG. 80.—Sporocyst of the Conical Amphistome resulting from the transformation and development of the embryo, age about fifteen days: *ex. p.*, excretory pore; *gg.*, matrix of germ cells. The large balls of cells represent developing redia of the next generation.  $\times 170$ . (After Looss, 1896, pl. 12, fig. 126.)

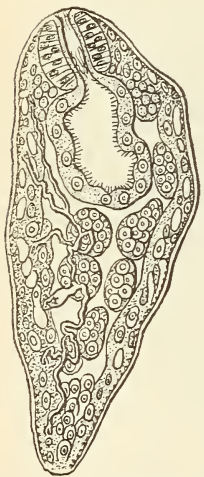


FIG. 82.—Young redia of the Conical Amphistome of the second generation in which the cercariae develop.  $\times 170$ . (After Looss, 1896, pl. 12, fig. 130.)



FIG. 83.—Mature cercaria of the Conical Amphistome (*Paramphistoma cervi*), the stage which gains access to cattle and sheep.  $\times 75$ . (After Looss, 1896, pl. 12, fig. 133.)

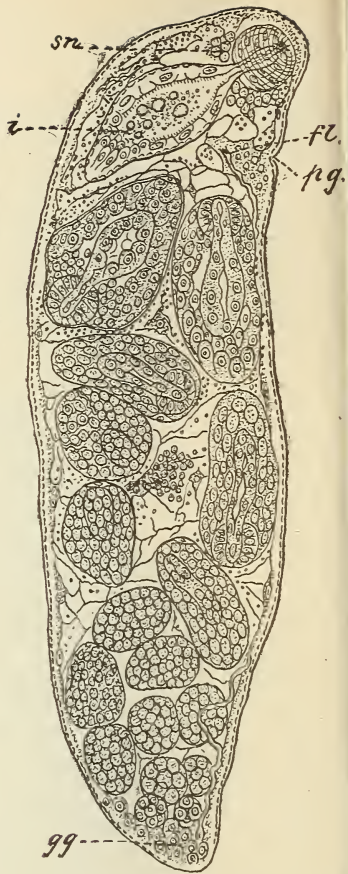


FIG. 81.—Adult redia of the Conical Amphistome (*Paramphistomum cervi*) of the first generation, thirty-nine days after the infection of the intermediate host with embryos: *fl.*, end portion of excretory system; *gg.*, matrix of germ cells; *i.*, rudimentary intestine; *gg.*, birth opening; *sn.*, nervous system. (After Looss, 1896, pl. 12, fig. 129.)

## VENAL DISTOMATOSIS.

Venal distomatosis is known as bilharziosis, or Egyptian hematuria. It is caused by flukes of the genus *Schistosoma*. As a matter of fact, the flukes themselves seem to be comparatively harmless; it is their sharp-pointed eggs which do the injury. At least three (imported) cases have been diagnosed in the United States, and the disease is said to exist in Cuba and Porto Rico.

**CLINICAL DIAGNOSIS.**—Make microscopic (low power) examination of fresh urine and feces to find the characteristic eggs or embryos; examine particularly the flocculi and clots found in the urine. In doubtful cases, have patient micturate and examine the last few drops forced out by straining.

**SYMPTOMS.**—If ova are confined chiefly to urogenital system: Hematuria, pains in lumbar region, left iliac fossa, thigh, or vulva, either spontaneous or at micturition; cystitis, vesical calculus, urinary fistulæ, vaginal tumors, nephritis. If ova are confined chiefly to rectum: Bloody stools, diarrhea, prolaps of rectum, papilliform growth which may require surgical interference.

**TREATMENT.**—Favorable results are claimed from repeated doses of male fern; some authors consider specific treatment futile; practically, treatment is the same as for chronic cystitis; occasionally surgical interference for polypoid growths.

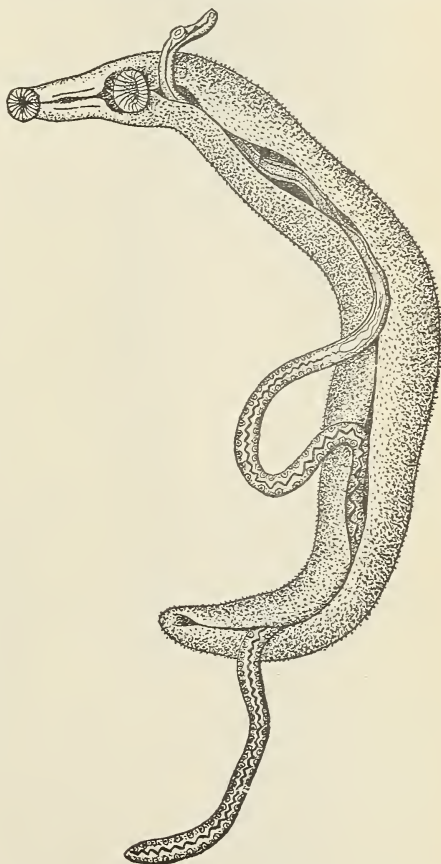


FIG. 84.—Male and female specimens of the Human Blood Fluke (*Schistosoma hæmatobium*), enlarged.  $\times 12$ . (After Looss, 1896, pl. 11, fig. 107.)



## Family SCHISTOSOMIDÆ.

Genus SCHISTOSOMA<sup>a</sup> Weinland, 1858.

GENERIC DIAGNOSIS.—Schistosomidæ (sexes separate): *Male*: Broad with ventrally curved lateral margins, forming the canalis gynæcophorus. Intestinal ceca unite some distance caudad of the acetabulum. *Genital pore* median, caudad of acetabulum. Copulatory organs absent; genital glands confined to a small area at the anterior end of canalis gynæcophorus; testicles composed of about five divisions; vesicula seminalis small, pars prostatica not evident. *Female*: Filiform. Uterus very long; may contain numerous eggs, with terminal or subterminal spine.

HABITAT.—Veins of mammals.

TYPE SPECIES.—*Schistosoma hæmatobium* (Bilharz, 1852).

The Human Blood Fluke—SCHISTOSOMA HÆMATOBIUM<sup>b</sup> (Bilharz, 1852) Weinland, 1858.

[Figs. 84 to 88.]

SPECIFIC DIAGNOSIS.—*Schistosoma*. *Male*: Whitish, 4 to 15 mm. long, 1 mm. broad; anterior portion of body 0.6 mm. long. Oral sucker about same size as acetabulum, which is anterior, immediately caudad of bifurcation of intestine. Skin with numerous small warts. Esophagus short; intestinal ceca reunite caudad of testicles; caudally of acetabulum, 4 to 6 glandular testicular bulbs. *Female*: Whitish to dark red brown, 15 to 20 mm. long. Suckers as in male. Skin with minute spines. Intestine as in male,

<sup>a</sup>SYNONYMS. — *Schistosoma* Weinland, 1858; *Gynæcophorus* Diesing, 1858; *Bilharzia* Cobbold, 1859; *Thecosoma* Moquin-Tandon, 1860; *Schistosomum* R. Blanchard, 1895.

<sup>b</sup>SYNONYMS. — *Distomum hæmatobium* Bilharz, 1852; *Schistosoma*

FIG. 85.—Anterior portion of male Human Blood Fluke (*Schistosoma hæmatobium*), showing the anatomical characters: *ac.*, acetabulum; *gc.*, cerebral ganglion; *gl.*, glands of esophagus (*es*); *i.*, intestine; *nda.*, dorsal anterior nerve; *ndp.*, dorsal posterior nerve; *na.*, lateral anterior nerve; *nva.*, ventral anterior nerve; *nvp.*, ventral posterior nerve; *plv.*, lateral posterior nerve; *gp.*, genital pore; *t.*, testicles; *vs.*, vesicula seminalis. (After Looss, 1895, pl. 2, fig. 18.)

*hæmatobium* (Bilharz) Weinland, 1858; *Gynæcophorus hæmatobius* (Bilharz) Diesing, 1858; *Bilharzia hæmatobia* (Bilharz) Cobbold, 1859; (?) *Bilharzia magna* Cobbold, 1859; *Thecosoma hæmatobium* (Bilharz) Moquin-Tandon, 1860; *Distoma capense* Harley, 1864, nomen nudum; *Bilharzia capensis* Harley, 1864; *Bilharzia hæmatobia hominis* Kowalewski, 1895; (?) *Bilharzia hæmatobia magna* (Cobbold) Kowalewski, 1895; *Schistosomum hæmatobium* (Bilharz) Blanchard, 1895.

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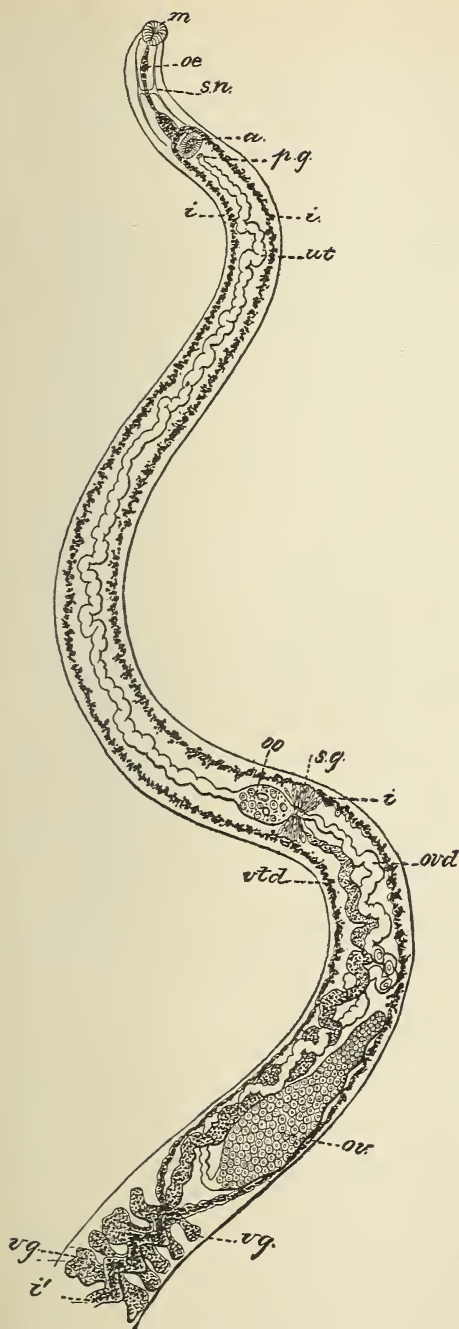


FIG. 86.—Anterior portion of female Human Blood Fluke (*Schistosoma haematobium*), showing the anatomic characters: *a*, acetabulum; *oe*, esophagus; *gp*, genital pore; *i*, intestine, which is double for some distance, but the two ceca unite (*i*) back of the ovary; *oo*., ootype; *ov*., ovary; *ovd*., oviduct; *sg*., shell gland; *sn*., nervous system; *ut*., uterus; *vtd*., vitelloduct; *vg*., vitelline glands.  $\times 38$ . (After Looss, 1896, pl. 11, fig. 108.)

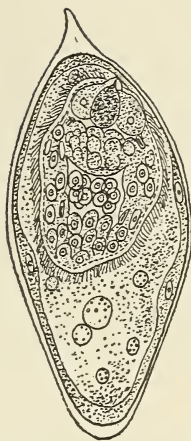


FIG. 87.—Egg of Human Blood Fluke (*Schistosoma haematobium*), with contained embryo, passed in the urine.  $\times 285$ . (After Looss, 1896, pl. 11, fig. 112.)



FIG. 88.—Ureter of an Egyptian, with numerous uric-acid concretions, as a result of blood-fluke infection. (After Leuckart, 1894, p. 528, fig. 231.)



but the ceca reunite caudally of, but near the ovary. Uterus rather straight, ends posteriorly in a bulb-like ootype, immediately posterior of which the shell gland, oviduct, and vitelloglands come together; ovary sacular, elongate; vitellaria extend from near the caudal end of the ovary to the caudal end of the body, and are provided with lateral acini. Eggs oval, 135 to 160  $\mu$  long by 55 to 66  $\mu$  broad; without operculum, but usually with terminal or subterminal spine; develop ciliated embryo in tissue after oviposition.

HABITAT.—Veins of man (*Homo sapiens*) and certain monkeys.

GEOGRAPHIC DISTRIBUTION.—Chiefly in Africa; sporadic imported cases in other countries.

WASHINGTON, D. C., August, 1903.

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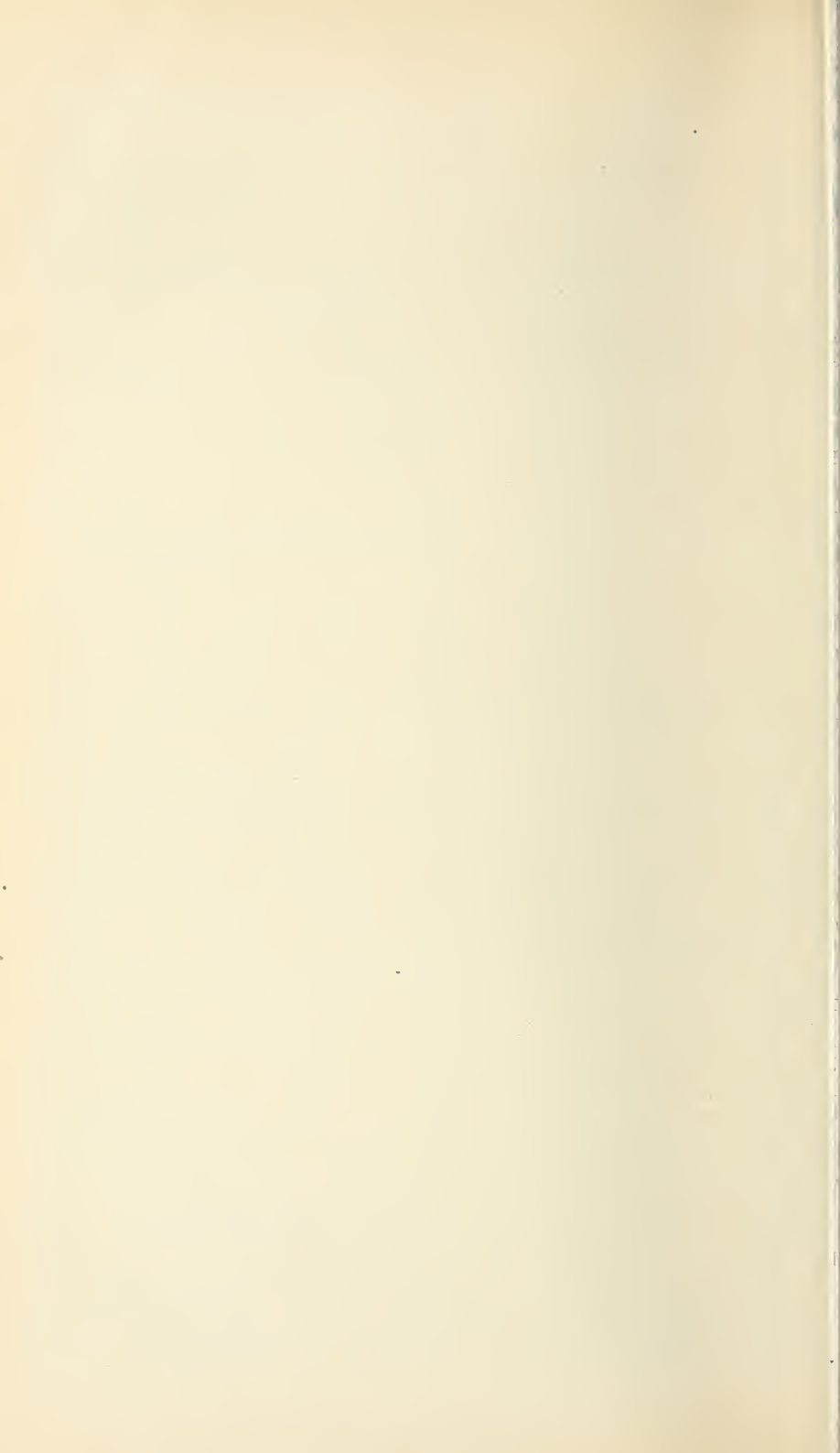
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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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*W. H. Ransom*  
HYGIENIC LABORATORY.—BULLETIN No. 18.

M. J. ROSENAU, Director.

September, 1904.

---

An account of the Tapeworms of the genus  
*Hymenolepis* parasitic in man,

INCLUDING

Reports of several new cases of the Dwarf Tapeworm  
(*H. nana*) in the United States.

BY

BRAYTON H. RANSOM.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.  
1904.

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# AN ACCOUNT OF THE TAPEWORMS OF THE GENUS *HYMENOLEPIS* PARASITIC IN MAN, INCLUDING REPORTS OF SEVERAL NEW CASES OF THE DWARF TAPEWORM (*HYMENOLEPIS NANA*), IN THE UNITED STATES.

(Prepared under the direction of CH. WARDELL STILES, Chief of Division of Zoology.)

By BRAYTON H. RANSOM, M. A.,<sup>a</sup>

Assistant in Division of Zoology, Hygienic Laboratory, United States Public Health and Marine-Hospital Service.

## SUMMARY.

The present paper comprises a full account, from both zoological and medical standpoints, of the representatives, three in number, of the tapeworm genus *Hymenolepis*, parasitic in man. This genus has received but slight attention from American authors. Recent indications, however, point to the probability that one species of this genus, *Hymenolepis nana*, the dwarf tapeworm of man and rats is, compared with other tapeworms, not an uncommon parasite of man in this country. Owing to its small size, and the necessity of depending for a diagnosis of its presence upon the discovery of its eggs in the feces by microscopical examination, it is undoubtedly frequently overlooked. About 100 cases altogether of this parasite have been reported from man.<sup>b</sup> Eleven cases have been found in this country during 1902-1903—in Texas, Georgia, South Carolina, and the District of Columbia.

The tapeworm in question was first described, upon the basis of specimens from rats, in 1845, by Dujardin, as *Tenia murina* [not Gmelin, 1790]; it was first noticed in man by Bilharz at Cairo, Egypt, in 1851, and a description under the name of *Tenia nana* was published by Siebold (1852). The earlier name, *T. murina*, had already been used for another form by Gmelin in 1790, and the name *nana* is accordingly retained as the correct specific designation.

It has been proved experimentally by Italian investigators that when eggs of this parasite are swallowed by white rats, the embryos hatch, bore into the intestinal

<sup>a</sup>Transferred June 1, 1903, to U. S. Bureau of Animal Industry, as Assistant Zoologist.

<sup>b</sup>Since the manuscript of this paper was finished, six more cases have been found by this laboratory in the District of Columbia, among 123 children in orphan asylums. Several probable cases have been reported to us by letter by Dr. J. B. De Velling, Jackson, Miss. Dr. L. E. Magnenat, of Amarillo, Tex., has found four cases in a single family (Stiles, 1903c). Finally Dr. H. M. Hallock (1904a), of the U. S. Army, has reported two cases at Fort Porter, Buffalo, N. Y., in soldiers recently returned from the Philippines. This makes altogether for the United States something over 25 cases, all but one having been recorded since August, 1902, and 16 of which have been found by members of this laboratory in a systematic examination for intestinal parasites of about 3,500 persons. It is significant that in these examinations only two cases of the beef-measle tapeworm, *Tenia saginata*, and none of the pork-measle



villi, become transformed into an intermediate stage (cercocysts), and later fall again into the lumen of the intestine to become adult. It is presumed that a similar development occurs in man, although the possibility remains that development, both in man and in the rat, may also occur by means of some intermediate host, such as an insect, not yet determined.

From the clinical side abstracts of 106 cases are given. Five of these are here reported for the first time.

Most of the cases have been in males and the large majority in children, commonly between the ages of 5 and 10 years.

Thirty-eight of the cases were found in the inmates of orphan asylums, a poor-house, and an insane asylum, and more cases have been reported from cities than from rural districts. Children in bad hygienic surroundings seem especially liable to infection, and institutional life seems to favor the occurrence of the dwarf tapeworm, both in children and in adults.

The prevalence of infection has been estimated as 10 per cent among the children of Italy. In the Government Hospital for the Insane, Washington, the parasite has been found in 0.3 per cent of about 2,000 patients examined. In about 160 fecal examinations recently made by Stiles (1903a) in the Southern States, the percentage of occurrence of *H. nana* was 0.25 per cent.

The largest number of cases from one State or country, 65, has been reported from Italy; the District of Columbia ranks second with 6 cases. The geographical distribution of the parasite as recorded for man accords very well with the distribution of the parasite as recorded for rats, and is practically cosmopolitan like that of its hosts.

The part of the intestine infected is the ileum.

The number of worms present in any one case varies from a single specimen to several thousand.

Simultaneous infection with other parasites is common. As many as four other species of parasites have been found occurring with *H. nana*.

Infection may persist from 2 months to 2½ years, perhaps to 5 years, and longer, or until terminated by successful treatment.

Comparison with statistics relative to larger tapeworms indicates that the symptoms produced by the presence of *H. nana*, while not more severe, apparently occur with greater frequency in a severe form in cases of *H. nana* than in cases of the larger tapeworms. This circumstance, however, is considered not to indicate a greater nocuity of the smaller worm; it is simply due to the fact that a relatively greater number of cases are overlooked.

The symptoms produced by the dwarf tapeworm are usually slight, and may be absent entirely, even though the worm be present in large numbers. Severe symptoms, however, such as persistent diarrhea, epileptiform attacks, etc., occasionally occur. The most frequent symptoms are abdominal pain, with or without diarrhea; convulsions of various sorts, frequently epileptiform; headache and strabismus. Nasal and anal pruritus, common in cases of infection with other tapeworms, are

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tapeworm, *Tænia solium*, were found. These facts continue not only to bear out the original assumption of Doctor Stiles that the dwarf tapeworm is going to prove a common American parasite, but seem to indicate, furthermore, the likelihood that it will turn out to be the most common of the tapeworms parasitic in man in this country.

In October and December, 1902, the examination of 60 children 1 to 15 years old, at a hospital in Buenos Aires, Argentina, showed 11 cases of infection with *H. nana*. (Lynch, 1904.) On a prior occasion 101 children were examined and no cases were found. Lynch considers the results of these examinations to indicate that the parasite is becoming more common in Argentina, and suggests the likelihood of many cases having been introduced by Italian immigrants, large numbers of whom have come into the country in recent years.



rarely seen with *H. nana*. A predisposition to nervous disease seems to be the important factor in the appearance of nervous symptoms.

The local pathological changes seem to be slight. The elimination of a toxin which is absorbed by the host possibly plays an important part in the production of morbose phenomena.

Diagnosis rests upon the discovery of eggs in the feces.

Treatment is with male fern and several repetitions are frequently necessary.

Prophylaxis consists in everything which will avoid the entrance of the eggs of the parasite into the mouth, as well as of insects, some of which may be able to serve as intermediate hosts and thus convey infection. It comprises the destruction of rats and mice; the protection of food from contamination by the excreta of rats; the exclusion of insects from the food; and general carefulness in regard to what is put into the mouth; especially should this last rule be enforced in the case of children, who commonly put into their mouths all sorts of objects, some of which, soiled by the excreta of infected persons or rats, may carry the eggs.

*Hymenolepis diminuta*, the flavopunctate tapeworm of man and of rats, was first described by Rudolphi, in 1819, from specimens collected in Brazil from rats. The same species was redescribed by Creplin (1825a) as *Tenia leptcephala*. It was first described from man by Weinland (1858), who did not recognize its identity and called it *Hymenolepis flavopunctata*.

Development occurs by means of an intermediate host, and several insects have been shown to act in this rôle; the common meal moth (*Asopia farinalis*), both in larval and adult stages, is perhaps the usual intermediate host.

Twelve cases have been reported from man, 3 in the United States, 2 in South America, and the rest in Europe.

Symptoms were practically absent in all the cases.

Diagnosis is established by the discovery of the eggs in the feces.

The worm seems to be easily expelled, and may pass without treatment. A simple cathartic has been efficient.

Prophylaxis consists in avoiding the ingestion of any of the various insects which may act as intermediate hosts.

*Hymenolepis lanceolata*, the lanceolate tapeworm of geese and ducks, has been recorded but once from man.

## INTRODUCTION.

Of the tapeworms parasitic in man there is one genus which is commonly overlooked in medical text-books, or at most passed over with only the slightest mention, namely, *Hymenolepis*. This genus, composed of a considerable number of species, is mostly restricted in its hosts to insectivorous mammals and birds, but three species, *Hymenolepis nana*, *H. diminuta*, and *H. lanceolata* have been also reported from man. The first of these, *H. nana*, is the most common of the three, and the most important. Like the larger tapeworms it is frequently the cause of severe symptoms, and indeed has been alleged by some authors to be productive of more serious effects than the former. In Italy, particularly Sicily, it seems to be one of the commonest parasites; some authors estimate that as many as 10 per cent of the children of certain classes in that country are infested by it. Its existence in the United States has been practically ignored on account of its apparent rarity, only 1 case until recently having been reported for this country. There is, however, some evidence to show that *H. nana* is considerably more common in the United States than generally supposed.

Owing to the small size of the tapeworm in question and the consequent necessity of depending for a diagnosis of its presence upon the discovery of its eggs in the feces, it seems very probable that it has been overlooked many times; and it is expected that as the microscope comes more generally into use as an aid in diagnosis of diseases, new cases of *H. nana* will come to light from time to time. Weight is given to these statements by the fact within the past year 11 new cases have been added to the single one formerly on record for the United States; namely, 1 in Texas by Dr. John T. Moore, 1 in South Carolina and 3 in Georgia by Dr. Ch. Wardell Stiles, and 6 in the District of Columbia by members of this laboratory.<sup>a</sup>

In the light of these recent developments *Hymenolepis nana* appears to merit more attention than it has hitherto received in this country, and Doctor Stiles has accordingly requested me to prepare a paper upon the genus *Hymenolepis*, taking into consideration such species as are of interest in human medicine. A paper similar to the present also seemed desirable from another standpoint; most of the literature is not generally accessible, being scattered in various foreign journals and in several languages; although Blanchard in 1891 published in French an excellent paper on the genus, which contained a complete résumé of the literature then extant, practically nothing has appeared

<sup>a</sup> For additional cases see footnote, p. 7.

in English, and altogether there is very little upon the group readily available to the American physician. In the preparation of this paper, practically the entire literature of *Hymenolepis* in man has been consulted, with the intention of bringing together everything that is known to date, regarding this genus in its relation to human medicine.

Genus HYMENOLEPIS<sup>a</sup> Weinland, 1858.

GENERIC DIAGNOSIS.—Family Tæniidæ, subfamily Dipylidiinæ: Head generally small; rostellum retractile, well developed and armed, or rudimentary and unarmed; suckers usually unarmed. Genital pores, single, marginal, unilateral. Testes few; usually three in each segment. Uterus sac-like; often filling the segment; frequently with outpocketings and incomplete partitions. Eggs with two, three or four membranes, the inner of which closely invests the embryo and may exhibit a small mamillate projection at each pole; the outer membrane is separated from the inner by a wide intervening space. Larva a cercocyst or staphylocyst.

TYPE SPECIES.—*Hymenolepis flavopunctata* Weinland, 1858=*H. diminuta* (Rudolphi, 1819).

The genus *Hymenolepis* was established by Weinland in 1858 with *H. flavopunctata* (= *H. diminuta*) as type, but was neglected almost entirely until rehabilitated by Blanchard in 1891. The characters of the genus as it now stands cover 30 or 40 species, some of which in many respects are widely divergent. It is therefore likely that in the course of time some of these species will be taken out of the genus and placed in new genera. Cohn (1899 c, e, g, 1900 b, 1901 b) has recently taken a step in this direction by proposing a division of the genus into two subgenera. In the subgenus *Hymenolepis* he would place those forms of the group which possess either an unarmed and rudimentary rostellum, or a rostellum armed with 20 to 30 hooks. In the second subgenus *Drepanidotænia* he would place forms possessing 8 to 10 hooks. According to this classification, *H. diminuta* and *H. nana* fall together in the first subgenus, and *H. lanceolata* in the second. There are, however, certain objections to this scheme of classification, one being that it is decidedly artificial and as such has been opposed by Wolffhügel (1899b, 1900 b) and also by myself in a former paper (Ransom, 1902). As an indication of the artificial nature of the proposed classification, it may be remarked that there are, in the group, tapeworms with 8 to 10 hooks which resemble, in the greater part of their anatomy, worms with rudimentary rostellum much more than they resemble other worms with 8 to 10 hooks; consequently, the use of a character, based upon the number of hooks, as a criterion in classification would often result in placing in one subgenus a species which, in all essentials except this one character, resembled the species typical of the second subgenus, more than it resembled the type of the first, and vice versa.

<sup>a</sup> SYNONYMS.—*Hymenolepis* Weinland, 1858; *Diplacanthus* Weinland, 1858 (not Agassiz, 1842, fish); *Lepidotrias* Weinland, 1858; "*Hymenolepsis*" of Osler, 1895, and other authors (misprint); "*Diplocanthus*" of Cohn, 1899 (misprint).

Although the plea of utility is an argument which might be advanced in favor of Cohn's division of the genus, it is, in fact, about the only argument, and moreover of little weight, since it is questionable whether such a division offers any advantages, even when viewed from a purely practical standpoint. While the character selected by Cohn as a distinguishing mark is certainly an easy one to use (though the loss of hooks from the rostellum might in some cases prove misleading), it does not seem to me that anything is to be gained by the separation of the various species now comprising the genus into the purely artificial groups proposed by Cohn, when it is almost certain that a revision will sooner or later be necessary, which will break up the genus along altogether different lines.

As there seems to be no sufficient reason, either from theoretical or practical considerations, for recognizing Cohn's division into subgenera, and as an attempt to revise the genus upon a rational basis is beyond the purposes of the present paper, if indeed such a revision could successfully be carried out at the present time, the three forms to be discussed will be regarded simply as belonging to the same genus, *Hymenolepis*, and the differences between them as of specific value only.

KEY FOR THE DETERMINATION OF THE SPECIES OF *HYMENOLEPIS* PARASITIC IN MAN.

- Strobila small, 5 to 45 mm. long, by 0.5 to 0.9 mm. wide, filiform; head armed with a crown of 20 to 30 hooks; eggs generally oval, with filaments attached to the poles of the inner membrane; common ..... *Hymenolepis nana*.
- Strobila 10 to 60 mm. long by 2.5 to 4 mm. wide; head unarmed; eggs generally round, prominent intermediate layer of albuminous substance between outer and inner membranes, outer membrane frequently with radial striations; rare ..... *Hymenolepis diminuta*.
- Strobila lanceolate, 30 to 130 mm. long by 5 to 18 mm. broad; head small, compared with strobila, armed with 8 to 10 hooks; eggs oval, without filaments on the inner membrane; very rare ..... *Hymenolepis lanceolata*.

The Dwarf Tapeworm—*HYMENOLEPIS NANA* <sup>a</sup> (Siebold, 1852) Blanchard, 1891.

SPECIFIC DIAGNOSIS.—*Hymenolepis*: Strobila 5 to 45 mm. in length, and 0.5 to 0.9 mm. in maximum breadth, composed of about 100 to 200 segments. Head subglobular, 130 to 480  $\mu$  in diameter; rostellum well developed, freely movable, armed with a single crown of 20 to 30 hooks, 14 to 18  $\mu$  in length; suckers globular, 80 to 150  $\mu$  in diameter. Neck long. Anterior segments very short; following segments increase in length and breadth, but remain broader than long, except that the length of the hindermost segments may occasionally equal or even slightly exceed

<sup>a</sup> SYNONYMS.—*Tænia murina* Dujardin, 1845 (not *T. murina* Gmelin, 1790 = *Cysticercus fasciolaris* Rudolphi); *Tænia nana* Siebold, 1852 (not Van Beneden, 1858); *T. ægyptiaca* Bilharz, 1852 (not Krabbe, 1869); *Diplacanthus nanus* (Siebold) Weinland, 1858; *T. (Hymenolepis) nana* Siebold of Leuckart, 1863; *T. "rana"* of Bell, 1886 (misprint); *Hymenolepis nana* Blanchard, 1891; *H. murina* Blanchard, 1891; "*Hymenolepsis*" *nana* of Osler, 1895, and other authors (misprint); *Tænia "minima"* of Huber, 1896 (misprint for *T. murina*).



their breadth. Genital pores on the left margin, near anterior border of each segment. Three testes in each segment; vas deferens enlarged to form a seminal vesicle within the cirrus pouch, while a seminal reservoir outside cirrus pouch is only slightly developed or absent. Gravid uterus occupies nearly the entire segment; wall of uterus with a few inconspicuous infoldings, forming incomplete partitions extending into the cavity of the uterus. Eggs number 80 to 180 in each segment; oval or globular; two distinct membranes; outer membrane 30 to 60  $\mu$  in diameter; inner membrane 16 to 34  $\mu$  in diameter, presenting at each pole a more or less conspicuous mamillate projection, provided with filamentous appendages; embryonal hooks 10 to 14  $\mu$  long.

HABITAT.—Small intestine of brown or Norway rat (*Mus decumanus*); black rat (*Mus rattus*); dwarf field mouse (*Mus minutus*); house mouse (*Mus musculus*); garden dormouse (*Eliomys quercinus*); and man (*Homo sapiens*).

DEVELOPMENT.—The embryo is swallowed, and after hatching enters a villus of the small intestine, where it transforms into a cercocystis, which in turn falls into the lumen of the intestine and becomes adult.

GEOGRAPHIC DISTRIBUTION.—Egypt, England, Italy, Sicily, Russia, Germany, Servia, France, Austria, Denmark, Siam, Japan, Pennsylvania, District of Columbia, Maryland, South Carolina, Georgia, Texas, Brazil, Argentina.

The Flavopunctate Tapeworm—HYMENOLEPIS DIMINUTA<sup>a</sup> (Rudolphi, 1819) Blanchard, 1891.

SPECIFIC DIAGNOSIS.—*Hymenolepis*: Strobila 10 to 60 mm. in length, 2.5 to 4 mm. in maximum breadth; composed of 800 to 1,300 segments. Head small, almost globular; 200 to 600  $\mu$  in width; rostellum rudimentary, pyriform, only slightly protractile; hooks absent; suckers globular, near the apical portion of the head, 80 to 160  $\mu$  in diameter. Neck usually short. Segments throughout strobila broader than long. Genital pores on left margin, near the junction of the anterior and middle thirds of each segment. Three testes in each segment; vas deferens dilates into a prominent seminal vesicle before entering the cirrus pouch, within which also is a vesicle. Gravid uterus occupies most of the proglottis; its cavity is subdivided into a large number of incompletely separated compartments filled with eggs. Eggs round or slightly oval; outer membrane 54 to 86  $\mu$  in diameter, yellowish in color, may be radially striated; inner membrane 24 by 20  $\mu$  to 40 by 35  $\mu$  in diameter, with mamillate projection at each pole often not apparent; between outer and inner membranes a prominent third layer of albuminous substance, often appearing as two delicate smooth membranes, with intervening space filled by a granular coagulum; embryonal hooks 11 to 16  $\mu$  in length.

HABITAT.—Adults in small intestine of brown or Norway rat (*Mus decumanus*); black rat (*M. rattus*); house mouse (*M. musculus*); Egyptian or roof rat (*M. rattus alexandrinus*); wood or field mouse (*M. sylvaticus*); *Rhipidomys pyrrhorhinus* [according to Linstow, 1878 a, p. 23]; and man (*Homo sapiens*).

<sup>a</sup>SYNONYMS.—*Tenia diminuta* Rudolphi, 1819; *T. leptcephala* Creplin, 1825; *Hymenolepis flavopunctata* Weinland, 1858; *Taenia (Hymenolepis) flavopunctata* Weinland, 1859; *H. (Lepidotrias) flavopunctata* Weinland, 1861; *T. flavomaculata* Leuckart, 1863; *T. "flavopuncta"* Weinland of Cobbold, 1864 (misprint); *T. "flariopunctata"* of Vogt, 1878 (misprint); *T. "flavopunktata"* of Stein, 1882 (misprint); *T. varesina* E. Parona, 1884; *T. minima* Grassi, 1886; *T. "septcephala"* of Perroncito & Airoidi, 1888 (misprint); *Hymenolepis diminuta* (Rudolphi, 1819) Blanchard, 1891; "*Hymenolepis*" *flavopunctata* of Osler, 1895, and other authors (misprint); *T. "varèrina"* Parona of Huber, 1896 (misprint for *T. varesina*); *T. "flavapunctata* of Simon, 1896 (misprint); *T. "leptocephala"* Previtera, 1900 (misprint); *T. ceptocephala* Lussana & Romaro [?date] (misprint); "*Tenia flavopunctata*" of Packard, 1900.



DEVELOPMENT.—The larval stage (*Cercocystis H. diminutæ*) occurs in larval and adult meal moths (*Asopia farinalis*); in young and adult earwigs (*Anisolabis annulipes*); and in adult beetles (*Acis spinosa* and *Scaurus striatus*).

GEOGRAPHIC DISTRIBUTION.—Massachusetts, Pennsylvania, Nebraska, Iowa, District of Columbia, Maryland, Brazil, Italy, Germany, France, Austria.

The Lanceolate Tapeworm—HYMENOLEPIS LANCEOLATA <sup>a</sup> (Bloch, 1782)  
Weinland, 1858.

SPECIFIC DIAGNOSIS.—*Hymenolepis*: Strobila lanceolate, 30 to 130 mm. long, by 5 to 18 mm. broad. Head compared with strobila very small; rostellum protractile, armed with single row of 8 hooks, 31 to 35  $\mu$  long. Neck short, often retracted with head into anterior portion of strobila. Segments much broader than long throughout the strobila. Genital pores on right-hand margin of segment near anterior border. Three testes in each segment; vas deferens enlarged to form a seminal vesicle, frequently S-shaped, before entering cirrus pouch; within latter, a second vesicle; vas deferens describes a complete loop in cirrus pouch before being transformed into the cirrus; cirrus freely protrusible, armed with spines. Female organs on opposite side of segment from genital pore; gravid uterus sac-like, with out-pocketings, filling most of the segment. Egg oval or spherical, with two thin membranes separated by an intervening space containing a small amount of albuminous substance; inner membrane occasionally with polar papillæ; outer membrane 50 by 35  $\mu$  to 100 by 100  $\mu$  in diameter; inner membrane 30 by 25  $\mu$  to 40 by 25  $\mu$  in diameter; embryonal hooks 8 to 15  $\mu$  in length.

HABITAT.—Adults in intestine of tame duck (*Anas boschas domestica*); black duck (*Anas obscura*); tame goose (*Anser anser domesticus*); muscovy duck (*Cairina moschata*); white-headed duck (*Erismatura leucocephala*); pochard (*Aythya ferina*); African teal (*Aythya nyroca*); red-crested pochard (*Aythya rufina*); flamingo (*Phenicopterus roseus*). Zschokke (1902) has recently reported one case in man (*Homo sapiens*).

DEVELOPMENT.—Not experimentally determined. Larval stage probably lives in small fresh-water crustacea.

GEOGRAPHIC DISTRIBUTION.—England, Denmark, France, Germany, and Austria.

The Dwarf Tapeworm—HYMENOLEPIS NANA (Siebold, 1852) Blanchard, 1891.

#### HISTORICAL REVIEW.

*Hymenolepis nana* was first discovered in man by Bilharz in 1851 at Cairo, Egypt, and the next year Siebold (1852) published a description, based upon letters from the discoverer, which translated reads as follows:

*Tænia nana* Sieb.<sup>b</sup>—It will not surprise us that among the many helminths which are found in man in the Nile countries there is also a special tapeworm. Bilharz discovered such a one and wished to call it after its native country, *Tænia ægyptiaca*;

<sup>a</sup>SYNONYMS.—*Tænia anserum* Frisch, 1727 [according to Rudolphi, 1810]; *T. anseris* Bloch, 1779 [according to Rudolphi, 1810]; *T. lanceolata* Bloch, 1782 (not *T. lanceolata* Chabert; not *T. lanceolata* Rosseter, 1891); *T. acutissima* Pallas, 1781, in part; *T. lanceola* Batsch, 1786; *Halysis lanceolata* (Bloch, 1782) Zeder, 1803; *Hymenolepis (Dilepis) lanceolata* (Bloch, 1782) Weinland, 1858; *Drepanidotænia lanceolata* (Bloch, 1782) Railliet, 1892; *Hymenolepis (Drepanidotænia) lanceolata* Cohn, 1899; *Tænia-Drepanidotænia lanceolata* (Bloch) Dadai, 1900.

<sup>b</sup>*Tænia nana* Sieb.—Es wird uns nicht überraschen, dass unter den vielen Helminthen, welche in den Nilländern den Menschen bewohnen, sich auch ein besonderer Bandwurm befindet; Bilharz hat einen solchen entdeckt und nach seinem Vaterlande

but, as it might develop later that the distribution of this parasite is not confined merely to Egypt, I have proposed for it the name of *Tenia nana*, as this tapeworm, through its smallness, contrasts extraordinarily with the other two tapeworms of man. That this small tapeworm is not perchance a torn or mutilated fragment may be asserted definitely, as I found many individuals uninjured and provided with a rounded last segment.

The first report upon this parasite I received from Bilharz, under date of May 1, 1851, in the following words:

“In the body of a boy who had died of meningitis there appeared after the first cut into the intestine a countless number of small tapeworms, *Tenia*, with broad segments completely formed, of the thickness of sewing thread, and hardly 10'' long. The head is large, its anterior surface smooth, quadrangular, and its corners formed by the round suckers located upon spherical eminences. In the posterior portion the head gradually grows narrower and tapers into the long slender neck. The segments found in succession behind the neck become gradually broader, until at the posterior end of the body they assume a breadth 3-4 times that of the head. This *Tenia*, moreover, occupied only a limited portion of the ileum.”

*Tenia aegyptiaca* benennen wollen, da es sich aber später herausstellen könnte, dass die Verbreitung dieses Parasiten sich nicht bloss auf Aegypten beschränkt, so habe ich für denselben den Namen *Tenia nana* vorgeschlagen, indem dieser Bandwurm gegen die beiden anderen Bandwurmart des Menschen durch seine Kleinheit ausserordentlich absticht. Dass dieser kleine Bandwurm nicht etwa ein abgerissenes oder verstümmeltes Bruchstück ist, lässt sich mit Bestimmtheit behaupten, da ich viele Individuen unverletzt und mit abgerundetem letzten Gliede versehen vorfand.

Die erste Nachricht über diesen Scharrotzer erhielt ich von Bilharz unterm 1. Mai 1851 mit folgenden Worten:

“In der Leiche eines an Meningitis verstorbenen Knaben zeigte sich mir nach dem ersten Schnitt in den Darm eine unzählige Menge eines kleinen Bandwurmes, einer *Tenia* mit breiten Gliedern, vollständig ausgebildet, von Nähfadendicke und einer Länge von kaum 10'''. Der Kopf ist gross, seine Vorderfläche eben, viereckig, die Ecken durch die runden, auf kugeligen Erhabenheiten stehenden Saugnäpfe gebildet. Nach hinten nimmt der Kopf allmähig an Breite ab und geht in den langen schmalen Hals über; die hinter dem Halse sich nach und nach einfindenden Glieder werden immer breiter, bis sie am Hinterende des Körpers die 3-4 fache Breite des Kopfes einnehmen. Diese *Tenia* nahm übrigens nur eine beschränkte Strecke des Ileum ein.”

Unterm 1. December schrieb mir Bilharz über diesen Bandwurm weiter:

“*Tenia nana* ist gewiss ein ausgewachsenes Thier. Ich habe die Eier am frischen Thier, das ich leider seit jenem Male nie wieder fand, beobachtet und auch in Weingeistexemplaren wieder erkannt. Sie sind kugelförmig, haben eine dicke gelbliche Schale, und zwar nur eine, wie mir scheint, doch zog sich der Inhalt der Eier unter dem Einfluss des Weingeistes kugelförmig zusammen, es mag daher noch eine dünne Dotterhaut vorhanden sein. Die sechs Häkchen der Taenien-Embryonen waren in den frischen Eiern deutlich zu sehen. Die Cirri finde ich, wie Sie es bereits bemerkt haben, alle auf einer und derselben Seite angebracht. Die Eier sind 1/00''' [sic] gross.”

Als Diagnose für diesen Bandwurm stellte Bilharz folgende Beschreibung hin:

*Tenia nana*.—Corpus filiforme, depressum, caput antice obtusum [sic], collum versus sensim attenuatum, acetabulis subglobosis rostello pyriformi uncinulorum bifidorum corona armato. Articuli transversi, cirri omnes unum eundemque marginem spectantes. Ovula globosa testa laevi simplici instructa.

Long. 6 lin.

Patria Aegyptus, in hominis intestino tenui semel reperta permagno.

Under date of December 1 Bilharz wrote me further with regard to this tapeworm:  
 “*Tænia nana* is certainly a full-grown animal. I observed the eggs in the fresh animal, which, unfortunately, I never have found again since that time, and also recognized them again in samples in alcohol. They are round like balls, have a thick yellowish shell, and indeed only one, as it appears to me; yet the contents of the eggs contract under the influence of the alcohol into a globular shape, hence

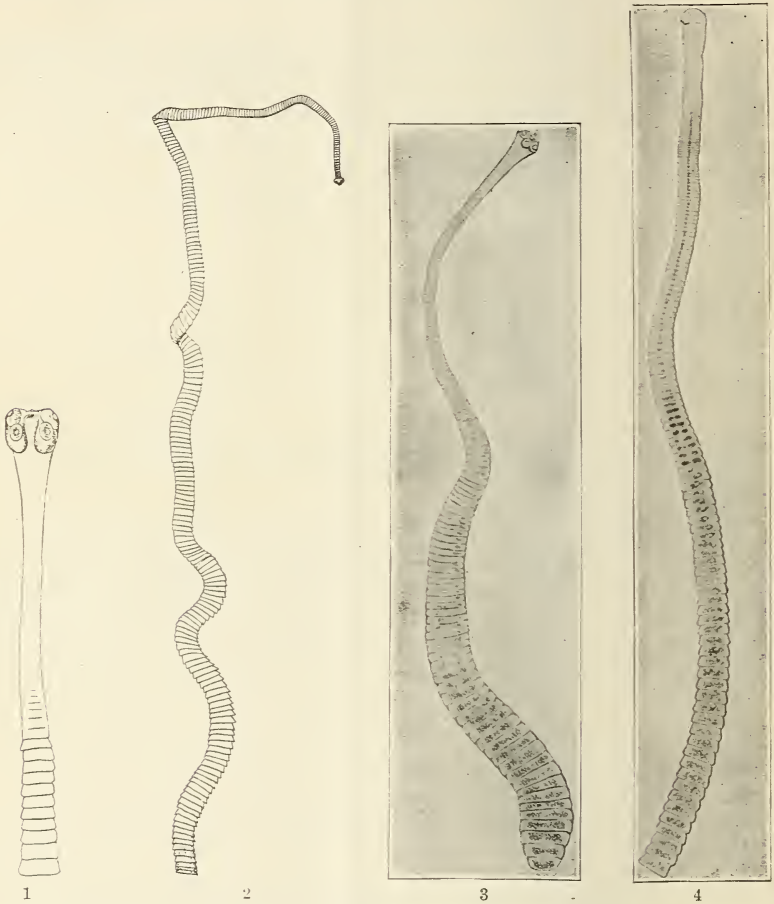


FIG. 1.—Original type figure of *Tænia nana* Siebold (= *H. nana*). Head and portion of strobila. Enlarged. (After Siebold, 1852, fig. 18.)

FIG. 2.—Original type figure of *Tænia murina* Dujardin (= *H. nana*). Head and portion of strobila. Enlarged. (After Dujardin, 1845a, pl. 12, fig. A1.)

FIG. 3.—Head and strobila of *H. nana*. Enlarged. (After Leuckart, 1863, p. 393, fig. 112.)

FIG. 4.—Head and portion of strobila of *H. nana*. Enlarged. (After Railliet, 1893, p. 293, fig. 190.)

there may be present also a thin yolk membrane. The six little hooks of the *Tænia* embryos were to be seen distinctly in the fresh eggs. I find the cirri, as you already have observed, all placed on one and the same side. The eggs are  $\frac{1}{100}$  in size.”

As a diagnosis for this tapeworm, Bilharz offered the following description:

*Tænia nana*: Body filiform, depressed; head obtuse anteriorly, gradually tapering into the neck, with almost globular suckers and pyriform rostellum armed with a



crown of bifid hooks. Segments broader than long, cirri situated all on one and same margin. Eggs globose, furnished with a single thin shell. Length, 6 lines.

Native country, Egypt; collected once in large numbers from the small intestine of man. (Translation).

Leuckart (1863) added to this brief account by a study of some of the original specimens, and more recently our knowledge of the anatomy has been further increased by Blanchard (1886a, e, f, 1891a), Grassi & Calandruccio (1887a), Mertens (1892), and a number of other observers.

Some years earlier than the first report of *Hymenolepis nana* in man, Dujardin (1845a, pp. 564-565, pl. 12, fig. A) reported from the rat, *Mus decumanus*, a new tapeworm, *Tænia murina* (not *Tænia murina* Gmelin, 1790 = *Cysticercus fasciolaris* Rudolphi, 1810), which seems in all respects to be identical with *Hymenolepis nana*, and is so considered by Grassi, Lutz (1894), Mingazzini (1898), Massari (1898), and others. The following is a translation of Dujardin's description:

*Tænia murina* Dujardin, *nov. sp.*<sup>a</sup>—Twenty-five mm. long, from 0.55 mm. to 0.9 mm. broad, composed of very numerous segments, four to eight times as broad as they are long; head 0.32 mm. broad, with a short thick rostellum surrounded by a simple crown of twenty to twenty-four hooks from 0.015 mm. to 0.017 mm. long; suckers 0.08 mm. broad; neck 0.15 mm. broad; first segments very short; the following (male) 0.07 mm. long, from 0.55 mm. to 0.6 mm. broad; the last filled with ripe eggs from

<sup>a</sup> *Ténia murin* (*Tænia murina* Duj., *nov. sp.*).—Long de 25 mm., large de 0 mm. 55 à 0 mm. 9, formé d'articles très nombreux, quatre à huit fois aussi larges que longs; tête large de 0 mm. 32, avec une trompe courte, épaisse, entourée d'une couronne simple de vingt à vingt-quatre crochets longs de 0 mm. 015 à 0 mm. 017; ventouses larges de 0 mm. 08; cou large de 0 mm. 15; premiers articles très courts; les suivants (mâles) longs de 0 mm. 07, larges de 0 mm. 55 à 0 mm. 6; les derniers remplis d'œufs murs longs de 0 mm. 15 à 0 mm. 17, larges de 0 mm. 8 à 0 mm. 9; tous les articles ayant leurs angles postérieurs un peu saillants, aigus, en dents de scie; orifices génitaux unilatéraux; testicule claviforme, étendu transversalement depuis le milieu jusqu'au réceptacle du pénis en forme de corne; pénis lisse, très grêle, peu saillant; œufs elliptiques à trois enveloppes; l'externe longue de 0 mm. 065; la moyenne membraneuse, plissée, longue de 0 mm. 05; l'interne plus résistante, un peu oblongue et terminée par une pointe obtuse à chaque extrémité; embryon long de 0 mm. 029 à 0 mm. 030, avec les crochets de 0 mm. 015 à 0 mm. 016.

Je l'ai trouvé, à Rennes, dans un surmulot (*Mus decumanus*), dans un mulot nain (*Mus pumilus*) [= *M. minutus*], et dans un lérot (*Myoxorus nitela*) [= *Eliomyz quercinus*].

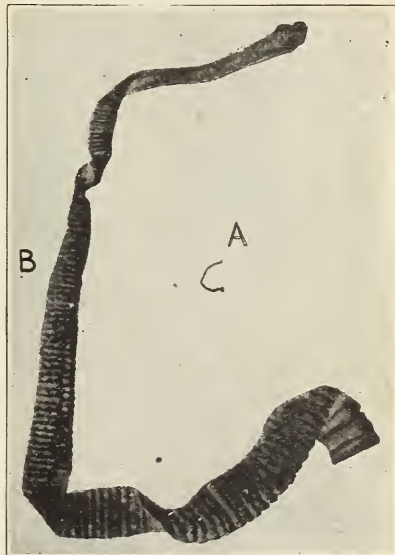


FIG. 5.—Head and strobila of *H. nana*. A, natural size; B, enlarged. (After Stein, 1882, pl. 12, figs. 9-10.)

0.15 mm. to 0.17 mm. long, from 0.8 to 0.9 mm. broad; all the segments having their posterior angles somewhat salient, sharp, shaped like saw teeth; genital orifices unilateral; testicle [misinterpretation of seminal receptacle] claviform, extending transversely from the middle to the receptacle of the penis in the shape of a retort; penis smooth, very slender, not very salient; eggs elliptical with three envelopes; the external one 0.065 mm. long; the middle one membranous, in folds, 0.05 mm. long; the internal one more resistant, somewhat oblong and terminating in an obtuse point at each extremity; embryo from 0.029 mm. to 0.030 mm. long, with hooks from 0.015 mm. to 0.016 mm. long.

I found it at Rennes in a brown rat (*Mus decumanus*), in a dwarf field mouse (*Mus pumilus*) [= *M. minutus*], and in a garden dormouse (*Myoxus nitela*) [= *Eliomys quercinus*]. (Translation.)

Blanchard (1891a), Moniez (1888), and Linstow (1896a) inclined to the opinion that the two forms *Tænia nana* and *Tænia murina* are distinct species. Blanchard (1896b), however, has more recently come to the conclusion that the slight inconstant differences which have been noted in the two forms are sufficiently accounted for by the difference in habitat, and that the two worms should be united under one species, which he would for reasons of priority call *Hymenolepis murina*. But since the name *Tænia murina* used by Dujardin, is preoccupied, having been applied before 1845 to another form, it can not be retained in this connection. *Tænia nana* Siebold, 1852 being the next available name, the correct designation of the species, placed in its proper genus, is therefore *Hymenolepis nana*.

Linstow (1896a) believed he found differences which would justify a specific distinction between the forms in man and in the rat, but, as Massari (1898) has pointed out, his results are not entirely free from criticism, and his arguments rather unconvincing.

*Hymenolepis nana* may, accordingly, be regarded as occurring not only in man, but also in the rat, and in the two hosts showing slight and variable differences, brought about by the action upon the parasite of an environment somewhat different in the two cases.

#### ANATOMICAL DESCRIPTION.

##### EXTERNAL ANATOMY.

As is well indicated by its name (*nana*, a dwarf) the worm under consideration is characterized preeminently by its small size (fig. 5A). Being also very delicate, and likely to be broken in pieces, it is thus a difficult matter to discover specimens in the feces, unless passed in large numbers.

*Strobila*.—Complete strobilæ with gravid segments may be found ranging in length from 5 or 6 mm. (Blanchard, 1891a) to a maximum, as recorded so far, in man of 35 mm. (Mertens, 1892). In the rat a length as great as 45 mm. has been observed (Stossich, 1898).

Favarcq (1894a) found a worm 75 mm. long, in the intestine of the garden dormouse (*Eliomys quercinus*), which he believed to be a



variety of *Hymenolepis murina* (Dujardin). This form possessed hooks somewhat similar to those of *Hymenolepis nana* (= *H. murina*), but as Favareq made no careful study of its anatomy, not even so far as to determine whether the genital pores were unilateral or alternating, the identity of the form remains doubtful.

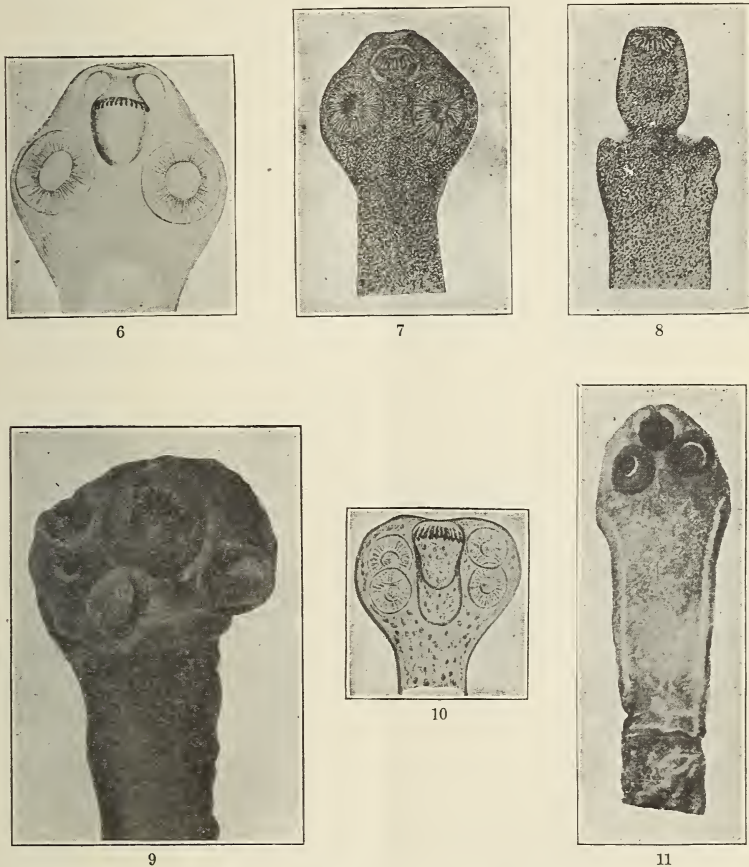


FIG. 6.—Head of *H. nana*. Enlarged. (After Leuckart, 1863, p. 394, fig. 113.)

FIG. 7.—Head of *H. nana*. Enlarged. (After Blanchard, 1886e, p. 328, fig. 3.)

FIG. 8.—Head of *H. nana* from which the suckers have been torn away. (After Blanchard, 1886f, p. 333.)

FIG. 9.—Head and neck of *H. nana*. Enlarged. (After Miura & Yamazaki, 1897, pl. 14, fig. 1.)

FIG. 10.—Head of *H. nana*. Enlarged. (After Mertens, 1896, fig. 2.)

FIG. 11.—Head and anterior portion of strobila of *H. nana*. Enlarged. (After Stein, 1882, pl. 12, fig. 11.)

Blanchard (1891a) considers 12 to 15 mm. the normal length in man, with a maximum breadth of 0.5 to 0.7 mm. The number of segments ranges from about 110 to 200; in the latter case 40 to 50 of the posterior segments contain fully formed embryos; in the former only the last 8 to 12 segments are gravid. A complete specimen measuring 12.5 mm. possessed 162 segments.

Mertens (1892) found the average length of a number of specimens to be over 20 mm., and the maximum breadth from 0.7 to 0.9 mm. The number of segments varied from 180 to 200, and this character was more or less constant, even with a variation of 3 to 4 mm. in the length.

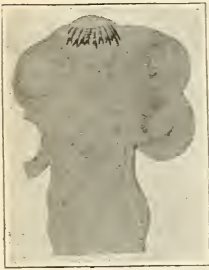
Miura & Yamazaki (1897) give a length of 20 mm., and a maximum breadth of 0.48 to 0.86 mm., measured in the fresh state, 0.3 to 0.56 mm. after preservation.



12



13



14



15

FIG. 12.—Head of *H. nana*. Enlarged. (After Krantz from Küchenmeister & Zürn, [1881], pl. 5, fig. 2.)

FIG. 13.—Head of *H. nana* with protracted rostellum. Enlarged. (After Krantz from Küchenmeister & Zürn, [1881], pl. 5, fig. 3.)

FIG. 14.—Head of *Taenia murina* Dujardin (= *H. nana*). Enlarged. Original type figure. (After Dujardin, 1845a, pl. 12, fig. A3.)

FIG. 15.—Head of *T. murina* Duj. (= *H. nana*) with protracted rostellum. Enlarged. Original type figure. (After Dujardin, 1845a, pl. 12, fig. A2.)

Dujardin (1845a) gives a length of 25 mm., and a maximum breadth of 0.55 to 0.9 mm., from specimens from rats; Grassi & Calandruccio (1887a), a length of 33 to 40 mm.; according to Linstow (1896a), incomplete specimens measured 23 mm., with a maximum breadth of 0.82 mm.

*Head.*—The head (figs. 1, 6–15) is more or less globular, flattened dorso-ventrally, and when viewed in front is somewhat rectangular, with its suckers at the four rounded angles. Its size has been given by various observers from 215 to 480  $\mu$  in width and 360 to 450  $\mu$  in length. It is often difficult, however, to tell where the head ends and the neck begins, especially in certain states of contraction, so that it is not always possible to determine the length with any degree of accuracy. Examples from the rat give measurements falling within the limits noted above. In specimens both from man and from the rat, measured

in this laboratory, the head has ranged in width from 130 to 250  $\mu$ .

*Suckers.*—The suckers, globular in shape, measure from 90 to 150  $\mu$  (Mertens, 1892). In specimens from the rat they seem to be generally smaller—according to Dujardin (1845a) 80  $\mu$ , and after Linstow (1896a), 79  $\mu$ , in diameter, while we have seen them here, in sizes from 70 to 90  $\mu$ , measured after preservation. In the live worm they are very protractile, and may be extruded to a considerable distance (Grassi & Calandruccio, 1887a). When thus extruded they may be torn away and

give rise to an anomaly (fig. 8) first described by Blanchard (1886f), and also noticed by Grassi & Calandruccio (1887a).

*Rostellum*.—Besides suckers the head possesses another organ of attachment, namely a protractile and freely movable rostellum (figs. 6, 7, 9–15), armed with hooks. In preserved material the rostellum is usually found retracted, but in material which has been fixed while still living, or in the live worm itself, is often seen extruded.

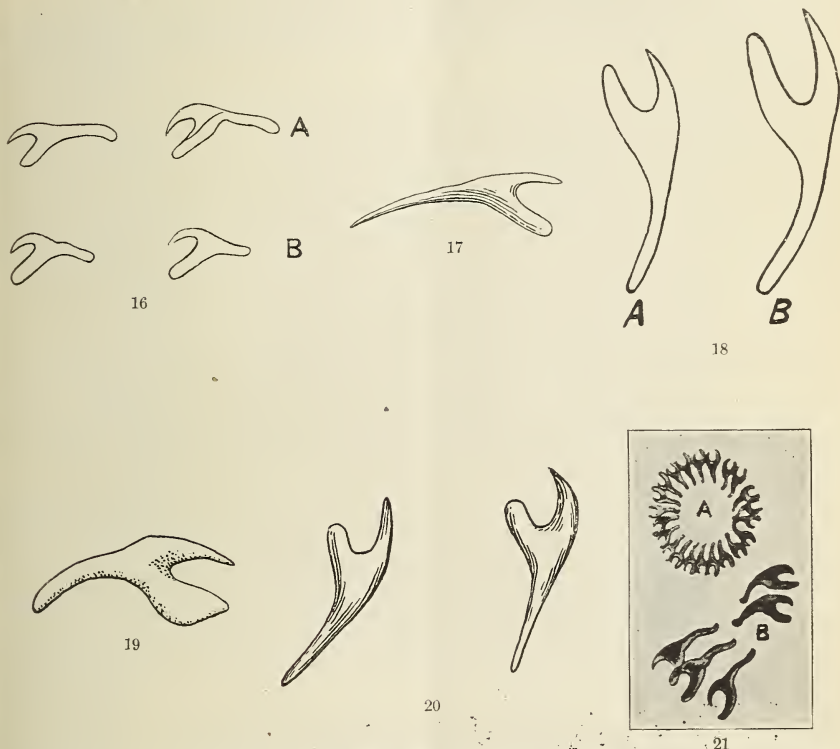


FIG. 16.—A. Hooks of *T. murina* Dujardin (= *H. nana*) from rat (*Mus decumanus*). Enlarged. (After Krabbe, 1865, pl. 3, figs. 56–57.) B. Same from mouse (*Mus musculus*). Enlarged. (After Krabbe, 1865, pl. 3, figs. 58–59.)

FIG. 17.—Hook of *H. nana*. Enlarged. (After Leuckart, 1886a, p. 996, fig. 409B.)

FIG. 18.—Hooks of *H. nana*. A, from man; B, from the rat. (After Linstow, 1896a, figs. iii and 3.)

FIG. 19.—Hook of *H. nana*. Enlarged. (After Railliet, 1893, p. 291, fig. 191.)

FIG. 20.—Hooks of *H. nana*. Enlarged. (After Mertens, 1892, fig. 3)

FIG. 21.—Hooks of *H. nana*. A, complete crown; B, isolated hooks. Enlarged. (After Krantz from Küchenmeister & Zürn, [?1881], pl. 5, fig. 4.)

*Hooks*.—The hooks (figs. 16–21) are arranged in a single row around the anterior part of the protrusible portion of the rostellum. Their number seems to be rather variable, with a range, putting together the numerous recorded observations, of 20 to 30. Leuckart (1863) gives 22 to 24 and (1886a, p. 997) 24 to 28; Rasch (1894) 22; Miura & Yamazaki (1897) 23; Zograf (1893) 23 to 28; Grassi & Calandruccio (1887a) 24 to 28; Linstow (1896a) 24; Moniez (1888), in eight specimens,



found seven with 24 to 26 hooks, one with 30; Blanchard (1891a) gives 24 to 28 as the normal number. All of these observations were made upon specimens from man, while specimens from the rat, according to Dujardin (1845a) and Krabbe (1865) possess 20 to 24; Linstow (1896a) finds 23 to 24. The hooks possess a rather long, somewhat curved dorsal root, directed forward on the rostellum, and, directed backward, a thick, heavy ventral root which is about equal in length to the sharp pointed prong, forming with it a sort of fork.

The roots of the hooks are more or less deeply embedded in the surface of the rostellum, and according to Mingazzini (1899) possess their own musculature, namely, fibers which are found in the inner sac of the rostellum.

The size of the hooks has been given as 14 to 18  $\mu$ . Krabbe (1865) gives the size in worms from the rat and mouse as 10 to 13  $\mu$ , but no other observer has found them so small. Linstow (1896a) would draw a distinction between the hooks of the worms as found in man and in the rat, but comparisons made in this laboratory of forms from both hosts show them identical both in shape and size.

*Neck*.—The neck (fig. 11) usually is slender, and somewhat less in diameter than the head, but this character varies with the state of contraction. Its width may be defined by the limits 80 and 300  $\mu$ , and its length to the first appearance of segmentation, 80  $\mu$  and 1 mm. or more.

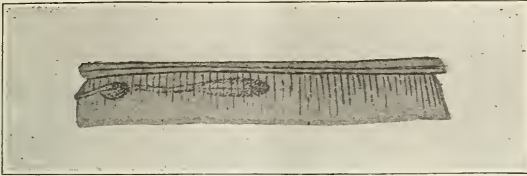
*Segments*.—As usual in tapeworms, segmentation is at first very indistinct. The segments are broader than long, and trapezoidal. The posterior border of each segment thus projects laterally beyond the anterior border of the following segment, making the edge of the strobila serrate. The younger segments are 6 to 10 times broader than long, a ratio which decreases toward the posterior end. Occasionally some of the posterior segments are seen stretched out so that their length exceeds their breadth. The width of the strobila gradually increases toward the posterior end, at or near which it reaches the maximum size already given. The last few segments may gradually decrease in width, and in a complete worm the last one is rounded off (figs. 3, 30).

*Genital pore*.—The genital pores (figs. 22–24, 28, 31–33) are located toward the anterior border of the segments, one in each segment, and all upon the left side, except as occasionally one is found upon the right side.

#### INTERNAL ANATOMY.

As in all cestodes, the spaces among the various organs are filled with a connective tissue known as *parenchyma*. *Calcareous corpuscles*, often large and present in great numbers amid the parenchymatous tissue of tapeworms, are comparatively small and few in *H. nana*.

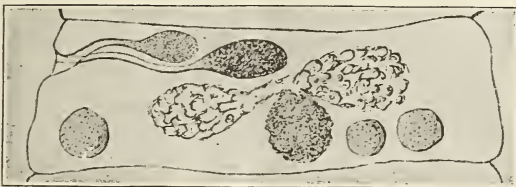
**ROSTELLUM.**—The rostellum is a sac-like body embedded in the axial portion of the head between the four suckers. Its wall is formed by a membrane which is continuous with the cuticula at the anterior



22



23



24

FIG. 22.—Proglottid of *T. murina* Duj. (= *H. nana*). Enlarged. Copy of original type figure. (After Dujardin, 1845a, pl. 12, fig. A5.)

FIG. 23.—Proglottids of *H. nana*: *a*, showing ovary; *b*, containing eggs in course of formation; *c*, gravid. (After Leuckart, 1863, p. 396, fig. 114.)

FIG. 24.—Proglottid of *H. nana* showing reproductive organs. Enlarged. (After Leuckart, 1886a, fig. 409A.)

surface of the head. The protrusible portion is occupied by a second smaller sac likewise limited by a membrane. Upon retraction the anterior part of the rostellum containing the inner sac is drawn



backward into the posterior part by the action of muscle fibers which extend longitudinally between the inner surface of the outer sac and the base of the inner sac. The anterior part of the rostellum is thus telescoped, so to speak, into the posterior part (fig. 10). Both the outer and the inner sac are filled by a loose parenchymatous tissue; they are each supplied with longitudinal and circular fibers in immediate relation with their walls, besides numerous longitudinal fibers extending through the parenchyma. Zograf (1893) considers the mass of the rostellum to be made up of fibers running in a spiral direction. Mingazzini (1899) does not find any circular fibers, but considers longitudinal fibers only to be present, the relations of which are changed in different states of protraction or retraction of the rostellum so that they sometimes present the appearance of circular or spiral fibers. Numerous muscle fibers also extend in various directions from the outer sac through the head. The size and relative dimensions of the rostellum are, naturally, somewhat variable. Leuckart (1886a, p. 997) gives its size as  $100\ \mu$  long by  $88\ \mu$  wide. According to Blanchard (1891a) it measures  $100\ \mu$  long by 80 to  $95\ \mu$  wide. Miura & Yamazaki (1897) find it  $56\ \mu$  long, and Mertens (1892) gives its size in the retracted state as 130 to  $140\ \mu$  long by  $80\ \mu$  wide. Measurements made in this laboratory of two specimens, in one of which the rostellum was protruded, in the other retracted, are as follows: First specimen, protruded portion of rostellum,  $48\ \mu$  long by  $60\ \mu$  wide; remainder of rostellum  $100\ \mu$  long by  $80\ \mu$  wide. Second specimen, rostellum,  $124\ \mu$  long by  $60\ \mu$  wide; protrusible portion,  $50\ \mu$  long by  $40\ \mu$  wide.

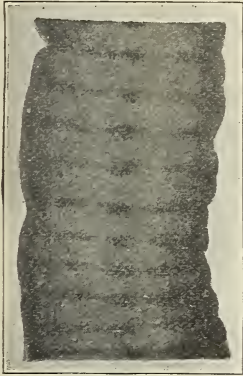
**NERVOUS SYSTEM.**—Two main lateral *longitudinal nerves*, one on either side, may be distinguished running through the entire strobila and united in the scolex by a ganglionic commissure posterior of the rostellum. As Mingazzini (1899) noticed, there are sometimes apparent in the posterior third of the rostellum two masses of cells, one on either side. These cells are evidently *nerve cells* and are similar to those found in the same situation in *H. diminuta* and *H. carioca* (Zschokke, 1889; Ransom, 1902). The position of the lateral nerves in the segment is the usual one among the Taniidæ, namely, a short distance laterad from the excretory vessels (*m. l. n.*, figs. 32, 33).

**MUSCULAR SYSTEM.**—The muscular system is only weakly developed. Beneath the cuticula lie the usual *subcuticular muscular fibers*—an *outer circular* and an *inner longitudinal* layer.

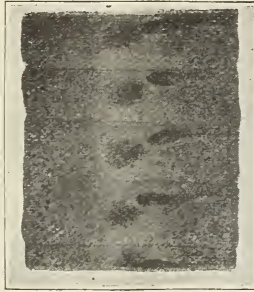
The main part of the muscular system consists of a layer of *longitudinal fibers* lying in the parenchyma, not far removed from the cuticula and separating the segment into a central and a cortical portion.

Linstow (1896a) maintains that in *Hymenolepis nana* from man (fig. 32) the cortical portion is, in respect to the thickness of the seg-

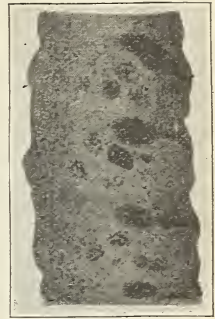
ment, relatively much thicker than in the form from the rat (fig. 33), which is one of his reasons for viewing the forms as distinct species. This character, however, is very inconstant, and varies with the manner of preservation of the material, and with the age and state of contraction of the segments. The layer of longitudinal fibers is to be



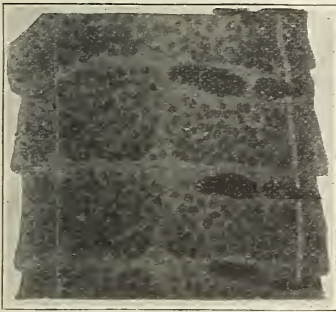
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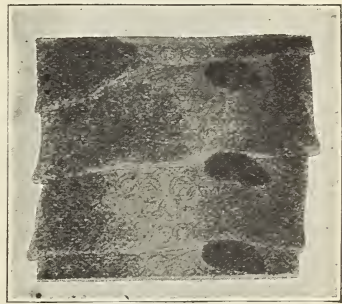
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28



. 29

FIG. 25.—Portion of strobila of *H. nana*, 1 mm. behind head; drawn with camera lucida from fresh material. Showing formation of segments begun, and primordia of reproductive organs. Enlarged. (After Miura & Yamazaki, 1897, pl. 14, fig. 2.)

FIG. 26.—Proglottids of *H. nana* with cirrus pouch and ovary; drawn with camera lucida from fresh material. Enlarged. (After Miura & Yamazaki, 1897, pl. 14, fig. 3.)

FIG. 27.—Proglottids of *H. nana*, showing cirrus pouch, seminal receptacle, ovary, and testes; drawn with camera lucida from stained preparation. Enlarged. (After Miura & Yamazaki, 1897, pl. 14, fig. 4.)

FIG. 28.—Proglottids of *H. nana*, showing cirrus pouch, seminal receptacle, immature ova, lateral longitudinal excretory canals; camera lucida drawing of stained preparation. Enlarged. (After Miura & Yamazaki, 1897, pl. 14, fig. 5.)

FIG. 29.—Gravid proglottids of *H. nana*, with prominent seminal receptacles; camera drawing of fresh material. Enlarged. (After Miura & Yamazaki, 1897, pl. 14, fig. 6.)

regarded as derived in part from the longitudinal subcuticular muscle fibers of the scolex and neck, in the manner described by Lühe (1894, 1896) for *Anoplocephala perfoliata* and other forms, also for *Hymenolepis carioca* (see Ransom, 1902). Longitudinal fibers, which in these regions form part of the subcuticular muscle system, as they pass backward, sink inward away from the cuticula, increase in size

and in their new position make up the mass of the longitudinal muscle layer. *Transverse muscle fibers*, if present, are very few and weakly developed. *Dorso-ventral fibers* are likewise insignificant.

**EXCRETORY SYSTEM.**—There are two pairs of lateral longitudinal excretory vessels (figs. 32, 33) which unite in the scolex to form an anastomosis at the base of the rostellum. Two small closed loops extend into the latter, one on either side (Mingazzini, 1899), similar to the loops found in *Hymenolepis diminuta* (p. 88) and *Hymenolepis*



30



31

FIG. 30.—Posterior end of *H. nana* with sterile proglottid (third from top); camera drawing of stained preparation. Enlarged. (After Miura & Yamazaki, 1897, pl. 14, fig. 7.)

FIG. 31.—Portion of strobila of *H. nana*. Enlarged. (After Stein, 1882, pl. 12, fig. 12.)

*carioca* (see Ransom, 1902). The ventral vessels are larger than the dorsal throughout the strobila, and are united in the posterior portion of each segment by a transverse vessel.

**REPRODUCTIVE SYSTEM.**—The sexual organs become evident as indistinctly defined masses of cells shortly after the first apparent strobilation (fig. 25). Toward the middle of the worm they are in a state of active sexual maturity. The male organs develop much more rapidly than the female organs, and become active earlier. As is common among tapeworms, they occupy more especially the dorsal



part of the segment, while the female organs are more ventral in position.

*Male organs.*—Three *testes* (figs. 24, 32, 33) are present, the usual number in worms of this genus. They are situated near the dorsal surface, in the posterior portion of the proglottis. When at the height of their development, in the younger segments, they occupy the greater part of the central portion of the parenchyma. Normally two are on the right and one on the left of the median line. This position may be reversed, or rarely only two or as many as four or five may be present, as occurs also in *Hymenolepis diminuta* (p. 89).

*Vasa efferentia* from the three testes unite to form a *vas deferens* which enters the base of the cirrus pouch. The vas deferens just before reaching the latter is often dilated to form a small *seminal reservoir* (Blanchard, 1891a), as I have also noticed frequently in specimens both from man and from the rat.

The *cirrus pouch* (figs. 22-24, 26-28, 31, *c. p.*, figs. 32, 33) is a club-shaped organ with muscular walls situated near the anterior border of the segment, with its long axis directed transversely, or often somewhat obliquely backward (caudad) toward the genital pore. It lies on the dorsal side of the longitudinal nerve and the excretory canals (figs. 32, 33). Within the cirrus pouch the vas deferens dilates to form a *seminal vesicle*, and then narrows again to form a very slender tube which may be protruded through the genital pore (Leuckart, 1863), or, perhaps, as is common in tapeworms, and as occurs in *Hymenolepis diminuta* (p. 89), protracted into the vagina of the same segment.

*Female organs.*—The *vagina* (figs. 32, 33) lies on the ventral side of the cirrus pouch, between it and the excretory vessels and longitudinal nerve. It is at first narrow, but mediad from the base of the cirrus pouch, it is swollen into a large oblong *seminal receptacle* (figs. 22-24, 27-33), usually filled in adult segments with a highly refractive hair-like mass of spermatozoa, and for this reason very apparent and prominent. It is easily recognized in any mature segment even under low magnification, lying near the anterior border of the segment, and extending inward toward the median line a variable distance in different segments.

Posterior of the seminal receptacle lies the *ovary* (fig. 24, *ov.*, figs. 32, 33) elongated transversely and bilobed. The egg cells in the ovary measure 10 to 15  $\mu$ .

The *yolk gland* (fig. 24, *y. g.*, figs. 32, 33) is an ovoid body situated in the median line, toward the ventral surface of the segment and posterior of the ovary in the space between the backward prolongations of its right and left lobes. The cells of the yolk gland are small, 2 to 4  $\mu$  in diameter, strongly eosinophilic.

The so-called *shell gland* (*s. g.*, figs 32, 33) has the usual position between the ovary and yolk gland, on the dorsal side of the latter. It is composed of only a few cells, and is very small and insignificant. It must not be imagined that this tiny complex of a few small cells

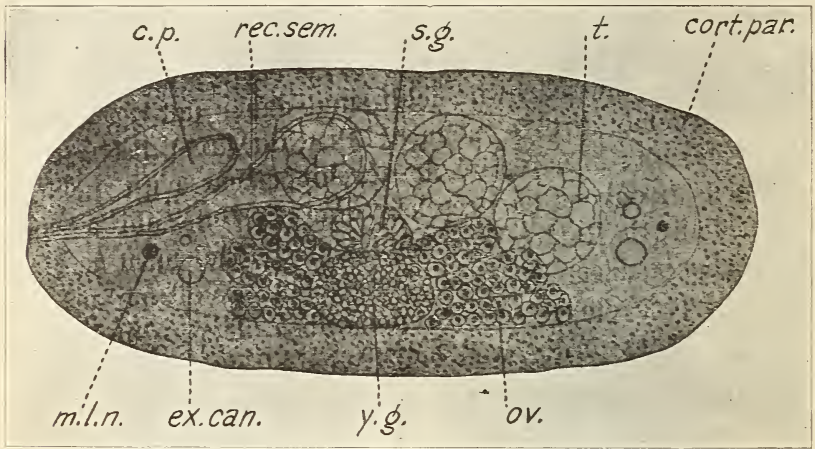


FIG. 32.—Cross section of proglottid of *H. nana* from man: *c. p.*, cirrus pouch; *cort. par.*, cortical parenchyma; *ex. can.*, excretory canal; *m. l. n.*, main lateral nerve; *ov.*, ovary; *rec. sem.*, receptaculum seminis; *s. g.*, shell gland; *t.*, testis; *y. g.*, yolk gland. Enlarged. (After Linstow, 1896a, fig. i.)

produces the material out of which the shells of the hundred or more eggs, contained in the gravid segment, are formed, which is a clear impossibility, since a single egg with its fully formed shell is much larger than the entire shell gland. The function of the shell gland in tapeworms in general has never been satisfactorily explained.

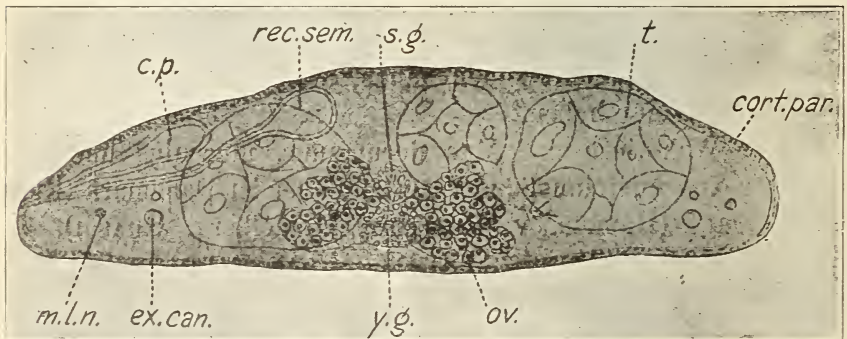


FIG. 33.—Cross section of proglottid of *H. nana* from rat. Lettering as in fig. 32. Enlarged. (After Linstow, 1896a, fig. 1.)

The *uterus* (fig. 23) develops very rapidly after sexual maturity is reached, the ovary disappears, and all the other organs, except the seminal receptacle and the cirrus pouch, degenerate completely or are masked and crowded out of sight by the uterus and its contained embryos. The uterus in the oldest segments occupies practically all



of the segment which is thus transformed into a mere egg sac. Blanchard (1891a) was of the opinion that the uterus is not bounded by a membrane, but that the eggs lie scattered throughout the entire parenchyma, so that the segment itself is, as it were, transformed into a uterus. That this idea is inexact, however, is readily apparent when one follows the development of the uterus in well-preserved material.

As in *Hymenolepis carioca* the uterus is at first simply a cellular mass elongated transversely, lying in front of the ovary (Ransom, 1902). This uterine primordium soon hollows out and takes on the appearance of a sac which rapidly fills with eggs and increases in size. Owing to the rapid and continued growth of the uterine wall, more pronounced in some places than in others, and owing to the obstacles by which the free expansion of the uterus is restricted, a modification from the condition of a simple sac-like uterus is brought about, a modification such as occurs in *Hymenolepis carioca*, and to a much greater degree in *H. diminuta* (p. 91). Instead of persisting as a simple sac the fully developed uterus has become a sac with infoldings, tubular processes, or invaginations extending inward among the eggs.

*Eggs.*—According to Blanchard (1891a) there are about 100 eggs in each segment; Mertens (1892) states 160 to 180; Leuckart (1886a, pp. 996–997) has counted 80. From the older segments eggs are continually escaping through ruptures in the walls.

Little is known with regard to the development of the eggs, but as first seen in the uterus they do not differ essentially in size (10 to 15  $\mu$ ) and appearance from eggs which are still in the ovary. A very delicate enveloping membrane may at times be distinguished. The egg begins to segment soon after it enters the uterus, and embryonic development proceeds rapidly. The embryo increases in size and a definite shell is formed.

As found in gravid segments or in the feces the egg (figs. 34–45) is oval, or occasionally spherical. The shell is very clear and transparent, but may take on a slight brownish or yellowish tint after standing for some time in the feces (Grassi, 1887d; Calandrucchio, 1890a; Mertens, 1892). It consists of two distinct membranes separated by an intervening space which contains a transparent substance, apparently fluid or semi-fluid and more or less finely granular. The *outer membrane* is very thin, less than 1  $\mu$  in thickness. The *inner membrane*, which closely invests the embryo or onchosphere as it is called, has



FIG. 34.—Egg of *T. murina* Duj. (= *H. nana*). Enlarged. Copy of original type figure. (After Dujardin, 1845a, pl. 12, fig. A6.)

FIG. 35.—Egg of *H. nana*. Enlarged. (After W. H. Ransom, 1856, p. 598, fig. 1.)

FIG. 36.—Egg of *H. nana*. Enlarged. (After Leuckart, 1863, p. 397, fig. 115.)

about the same thickness as the outer, but with a more distinct double contour (Mertens, 1892). At two opposite points, usually corresponding to the poles of the egg, the inner membrane has a small *mammillated projection*, often not apparent. To each of these projections are attached a number of clear *hyaline fibers*, resembling elastic fibers in appearance, which pass outward through the intermediate substance toward the outer membrane. Whether there is any constancy in the number of these filaments is not known. Mertens (1892) in observing an egg turned on end, saw at one pole as many as 8, converging like spokes in a wheel and attaching to the papilla of the inner membrane.



- FIG. 37.—Eggs of *H. nana* from mouse. Enlarged. (After Krabbe, 1865, pl. 7, fig. 108.)  
 FIG. 38.—Egg of *H. nana* from man. Enlarged. (After Bizzozero, 1889a, pl. 4, fig. g'.)  
 FIG. 39.—Eggs of *H. nana* from rat. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, figs. 1 and 2.)  
 FIG. 40.—Egg of *H. nana*. Enlarged. (After Mertens, 1892, fig. 1.)  
 FIG. 41.—Egg of *H. nana* from man. Enlarged. (After Linstow, 1896a, fig. iv.)  
 FIG. 42.—Egg of *H. nana* from rat. Enlarged. (After Linstow, 1896a, fig. 4.)

Beginning at the papillæ the filaments pursue an irregular, winding and convoluted course, gradually becoming more tenuous, but, so far as may be observed, do not branch, and end finally in the peripheral portion of the *intermediate substance* directly underneath the outer membrane. Two layers of slightly different appearance may often be distinguished in this intermediate substance, an inner portion which is clear and homogeneous, free from fibers except where it is penetrated by them in the two polar regions, and a thicker outer portion which is granular and in which the distal ends of the fibers interlace, forming an irregular meshwork. For a great part of their course

the fibers frequently follow the boundary between the clear and granular portions of the intermediate substance (Calandruccio, 1890a). According to Mertens (1892) the fibers do not attach to the outer membrane, since this may be split off and the intermediate layer remain undisturbed. The peripheral portion, at least, of the intermediate substance seems thus to possess a certain solidity as though bounded externally by a membrane, which must, however be very thin, separating it from the outer membrane. Mertens (1892), indeed, states that

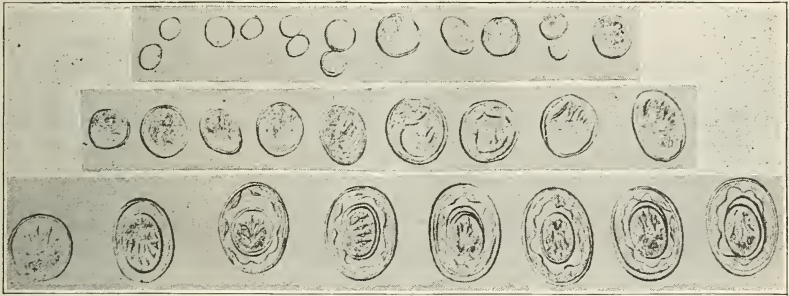


FIG. 43.—Eggs of *H. nana* and spherical bodies, perhaps eggs in course of development. Enlarged. (After Senna, 1889, fig. 2.)

he has observed at times a very thin homogeneous layer between the intermediate substance and the outer membrane, and I have occasionally noted a similar appearance. It frequently happens that the intermediate substance shrinks away from the outer membrane, or from the inner membrane, or from both. This results in the appearance of a third membrane intermediate between the other two, as occurs under similar circumstances in the egg of *H. diminuta*, (p. 93). As in *H. diminuta*, also, there are 3 or 4 comparatively large nuclei (visible in



FIG. 44.—Eggs of *H. nana*. Enlarged. (After Senna, 1889, fig. 1.)

sections) present in the intermediate substance which seem to play a part in the formation of the shell. W. H. Ransom (1856) and Senna (1889) describe a concentric striation of the intermediate substance. Grassi (1886b, 1887d) was the first to observe the filaments which he described as a long convoluted thread apparently attaching to the poles of the inner membrane. Blanchard (1891a) considers that Grassi (1886b, 1887d) and Senna (1889) were in error regarding the presence of filaments, and that they had erroneously interpreted folds or wrinkles of a third membrane. That filaments are present is a well-established fact, however, attested by a number of observers. The three pairs of



hooks with which the onchosphere is supplied are usually found directed toward one pole (Mertens, 1892; Miura & Yamazaki, 1897, and others), and as has been pointed out in other tapeworms (Siebold, 1854; Ransom, 1900), the middle pair differ from the other by being more slender and without a definite ventral root.

Various *sizes* have been assigned to the eggs, and there is, in fact, considerable actual variation. Bilharz (Siebold, 1852) gives a diameter of 26  $\mu$ . Leuckart (1863, 1886a, p. 996) found them 40 to 58  $\mu$ . Grassi (1879h), 33 by 33  $\mu$  and 33 to 36 by 28 to 31  $\mu$ . Grassi & Calandruccio (1887a) 43 by 35  $\mu$  to 53 by 40  $\mu$ . Perroncito & Airoidi (1888a, b, c), outer membrane, 40 by 32  $\mu$  to 52 by 41  $\mu$ ; inner membrane, 24 by 20  $\mu$  to 34 by 24  $\mu$ . Mertens (1892), outer membrane, 33 by 39  $\mu$  to 45 by 60  $\mu$ ; inner membrane, 26 by 25  $\mu$  to 30 by 29  $\mu$ . Senna (1889), 40 by 36  $\mu$  to 50 by 40  $\mu$ . Linstow (1896a), outer membrane, 39 by 39  $\mu$  and 43 by 31  $\mu$ ; inner membrane, 28 by 28  $\mu$ . Blanchard (1891a), outer membrane, 30 to 37  $\mu$  by 48 to 55  $\mu$ ; inner membrane, 16 to 19  $\mu$ . According to my own measurements the outer membrane ranges from 36 by 32  $\mu$  to 56 by 42  $\mu$ ; the inner membrane from 18 by 20  $\mu$  to 24 by 32  $\mu$ . The onchosphere is 5 to 10  $\mu$  smaller than the inner membrane. The size



FIG. 45.—Egg of *H. nana*, as seen in fresh feces. Enlarged. (After Ransom, from Stiles, 1903a, p. 85, fig. 85.)

of the *embryonal hooks* has been given by various authors from 9 to 16  $\mu$ ; according to Blanchard (1891a), with whose figures mine agree, they measure 10 to 12  $\mu$ . From measurements of 9 eggs, Miura & Yamazaki (1897) give the following figures:

Outer envelope—Length: Maximum, 56.7  $\mu$ ; minimum, 41.3  $\mu$ ; mean, 50.7  $\mu$ . Breadth: Maximum, 53.2  $\mu$ ; minimum, 35.1  $\mu$ ; mean, 42.9  $\mu$ .

Inner envelope—Length: Maximum, 32.4  $\mu$ ; minimum 27  $\mu$ ; mean, 30.1  $\mu$ . Breadth: Maximum, 29.7  $\mu$ ; minimum, 24.3  $\mu$ ; mean, 25.9  $\mu$ .

Hooks of embryo—Maximum, 13.5  $\mu$ ; minimum, 10.8  $\mu$ ; mean, 12.9  $\mu$ .

As to the eggs of *Hymenolepis nana* from the rat, which some authors have considered larger than those of the form found in man, it may be said, in the first place, that the size of the eggs is a very variable character as the figures already given testify, and it is consequently doubtful if a satisfactory comparison could be instituted or any constant difference be discovered between the two forms in this regard; and in the second place, considering the great variability of this character, that it would be necessary to make measurements of a large number of examples, with due regard to similarity of conditions, etc., before one affirmed that the eggs were, even generally, larger or smaller in one case than in the other. Dujardin (1845a) gives the size

of the egg of *Tænia murina* (= *H. nana*) from the rat as 65  $\mu$ ; Linstow (1896a), 49 by 42  $\mu$  to 54 by 47  $\mu$ ; measurements which I have made range from 36 by 26  $\mu$  to 52 by 36  $\mu$ . With the exception of Dujardin's figures these sizes fall within the limits established for *Hymenolepis nana* from man.

Senna (1889) noticed in feces containing completely developed eggs of *Hymenolepis nana*, in six cases, numerous small rounded bodies (fig. 43) measuring from 5 to 10  $\mu$  to 30  $\mu$  in diameter. The smaller of these were homogeneous in appearance, tinted like mother-of-pearl, and bounded by a very thin membrane, while the larger were more granular and tended to become oval, with a thicker membrane, as indicated by a distinctly double contour. Senna was inclined to interpret these as eggs in course of development, which had prematurely escaped from the uterus, but since he found similar bodies in two cases in which he could not demonstrate the presence of *H. nana*, he was left in doubt with regard to their nature and significance.

#### DEVELOPMENT AND LIFE HISTORY.

The well known and usual mode of development of tapeworms of the family Tæniidæ, to which *Hymenolepis nana* belongs, is as follows:

The eggs containing six-hooked embryos pass out of the body of the definitive host in the feces. To develop further they must be taken into the alimentary canal of some other animal. If the conditions are suitable in this animal the embryos, after hatching, if this has not already taken place, bore out of the alimentary canal, and, encysted somewhere in the tissues of the body, develop into the intermediate stage, *cysticercus* or *cysticercoid*, as the case may be. When this animal, the intermediate host, is eaten by an animal which can act as a definitive host, the intermediate stage continues its development and becomes transformed into the *adult worm*, which produces eggs, thus completing the cycle. As one would expect, the normal intermediate host is an animal which is the natural food of the definitive host, or otherwise likely to be taken into the alimentary canal of the latter.

Leuckart (1863, pp. 395, 397), upon theoretical grounds, assuming that an interchange of hosts occurred during the life history of *Hymenolepis nana* and noticing the great similarity in the anatomical characters of the worm in question, of certain tapeworms from mice and shrew-mice and of a cysticercoid found by Stein in the meal worm,<sup>a</sup> expressed the opinion that the intermediate stage was developed in some insect.<sup>b</sup>

<sup>a</sup> Hooks very similar in form are found in the related tapeworms of our mice and shrew-mice, as well as in the cysticercoid of Stein from the meal worm. (Translation of Leuckart, 1863, p. 395.)

<sup>b</sup> We content ourselves \* \* \* with the supposition that, as in the most nearly related species, the worm passes its youth as a cysticercoid in some insect. (Translation of Leuckart, 1863, p. 397.)



The occurrence of the large numbers in which the worm is found in the human intestine he (Leuckart, 1886a; 1886b, p. 661) would explain as resulting from a budding of the cysticeroid in the intermediate host similar to that which takes place in cysticeroids (*Staphylocystis bilarius* and *S. micracanthus*) found by Villot (1878) in certain myriapods. Leuckart (1886a, p. 997) also considered the possibility of some snail being the intermediate host of *H. nana*, upon the basis of information that the children in the vicinity of Belgrade, where a case had been observed in a child (see case No. 6), very commonly ate a kind of little white snail.

Stein's cysticeroid (*Cercocystis tenebrionis* Villot, 1882 = *Cysticerus, tenebrionis* = *Scolex decipiens*) of the meal worm (larva of *Tenebrio molitor*) was considered by Leuckart (1880, pp. 420, 457) the probable intermediate stage of *Tænia murina* Dujardin (= *Hymenolepis nana*). Villot (1882), however, looked upon this cysticeroid as belonging to *Tænia microstoma* Dujardin, 1845, a tapeworm of the mouse, and Moniez (1888) and Linstow (in litt. Moniez, 1888) were of the same opinion.<sup>a</sup> Grassi (1887d) at first believed that this cysticeroid would prove to be the intermediate stage of *Hymenolepis nana*, but later abandoned this hypothesis and concurred (Grassi & Rovelli, 1889b, p. 371) in the opinion of Villot, Moniez, and Linstow.<sup>b</sup>

Grassi and Calandruccio (Grassi, 1887h) attempted numerous times under varying conditions to infest larvæ of *Tenebrio molitor* with eggs of *Hymenolepis nana*, but always without success. They also examined from those localities of Lombardy and Sicily in which they had found *Hymenolepis nana* common in man, hundreds of specimens of numerous species of arthropods, molluscs, and worms, especially edible molluscs, lice, flies, meal worms, the larvæ of certain beetles living in beans, etc., in the hope of finding a cysticeroid to correspond with *H. nana*. All of these investigations resulted negatively with the exception that two cysticeroids were found in a meal worm, which were fed to a man, with negative results. It was during this time that Grassi noticed the great frequency of *Hymenolepis murina* (Dujardin) in rats in Catania, where also from 250 examinations of children, rang-

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<sup>a</sup>It cannot be admitted that the cysticerus of the meal worm belongs to *Tænia nana*; this cysticerus possesses a crown of 30 hooks which have a length of 12  $\mu$ , while *T. nana*, as well as *T. murina*, presents only 24 hooks 15 to 18  $\mu$  long. In both these characters, on the other hand, the cysticerus of the meal worm corresponds with *Tænia microstoma* of the mouse, with which Villot has already associated it; von Linstow (in litt.) is of the same opinion, with which we can only agree after having examined attentively the head of the cysticerus and that of the adult animal. (Translation of Moniez, 1888.)

<sup>b</sup>The few experiments which Grassi and Rovelli performed, by feeding eggs of *Tænia microstoma* to larvæ of *Tenebrio molitor*, resulted negatively, and this supposed connection between the adult tapeworm and the cysticeroid in question is still not definitely established. (Grassi & Rovelli, 1892a, p. 78.)

ing from  $\frac{1}{2}$  to  $1\frac{1}{2}$  years, 20 cases of *H. nana* were found, and noticing the great similarity of the two forms, he was thus led to their identification, as one and the same species, or at most as scarcely distinguishable varieties of a single species. In view of the fact that, although *Hymenolepis nana* was so exceedingly common in these regions, no corresponding cysticeroid was to be found in the many animals examined, belonging to species which *a priori* might be considered possible intermediate hosts, Grassi then resorted to the idea of a direct development; and, indeed, experiments along this line resulted in a demonstration of the fact that the eggs of *Hymenolepis nana* from one rat when fed to another develop into mature worms in the intestine. Development, however, was found not to be direct, i. e., the embryo from the egg did not grow immediately into the form of the adult, but penetrating into a villus developed there into a cysticeroid, which in turn reentered the alimentary canal, to become transformed into the adult stage. The rat was thus shown to act not only as the definitive host, but also as the intermediate host. In spite of the evident exactness of the results of these experiments, and in spite of the probability that the cysticeroid (*Cercocystis tenebrionis*) of the meal worm is more likely the intermediate stage of *Tænia microstoma*, Leuckart (1887) still considered this cysticeroid the intermediate stage in the normal life cycle of *Hymenolepis murina* (= *H. nana*), and looked upon the development of an intermediate stage in the villus of the rat's intestine as unusual, and not of common occurrence in the natural order of things. The balance of evidence, however, seems to indicate that there is no connection between the above-named cysticeroid and *Hymenolepis nana*, but whether the eggs of the latter may not develop into a cysticeroid in some insect, as well as in the intestinal villi of the rat, is not known. So far as the direct evidence goes, however, the development as outlined by Grassi must be considered the normal and usual method.

The experiments by which the life history was determined are as follows (Grassi, 1887h; Grassi & Rovelli, 1892a):

Thirty-four white rats were used, aged from 1 to 3 months, kept in clean cages, closed, except on one side, which was covered with wire screen. After weaning, the rats were fed only with bread and pure water. The mothers were determined to be free from tapeworm, during lactation by examination of the feces, and afterwards by killing and examining post mortem. The experiments were repeated 11 times, each time by feeding 1 to 3 of the  $3\frac{1}{2}$  rats with mature segments of *Hymenolepis nana* from infected rats and placing them in separate cages, and also at the same time isolating 1 or 2 which had not been thus fed, in order that there might be a check on the results. Constantly among the former, *Hymenolepis nana* developed in greater or less number, sometimes more than 100; among the latter no specimens whatever were found.

The rapidity with which development occurred varied in different individuals. In general, after 4, 5, or 8 days, tapeworms 3, 5, or 8 mm. long were found—that is, either with simply a long neck, or with evident proglottids. After 15 days, tapeworms were found containing mature eggs; after 30 days, the eggs began to appear in the feces.

While the results in the experiments with white rats aged from 1 to 3 months were constant and positive, when rats younger than 1 month (suckling) or over 3 months were used the results were either negative or only a few tapeworms were developed. Ordinary rats proved more refractory to infection than white rats, and the results were generally negative, even when the rats were of the favorable age—1 to 3 months. Whether the animal was fasting or well fed, or whether many or few segments were given, had no effect on the results. Rats already harboring *Hymenolepis nana* also proved refractory to further infection.

It is in the villi of the last 10 to 12 cm. of the small intestine that the intermediate stage develops. As in *Oxyuris vermicularis*, however,



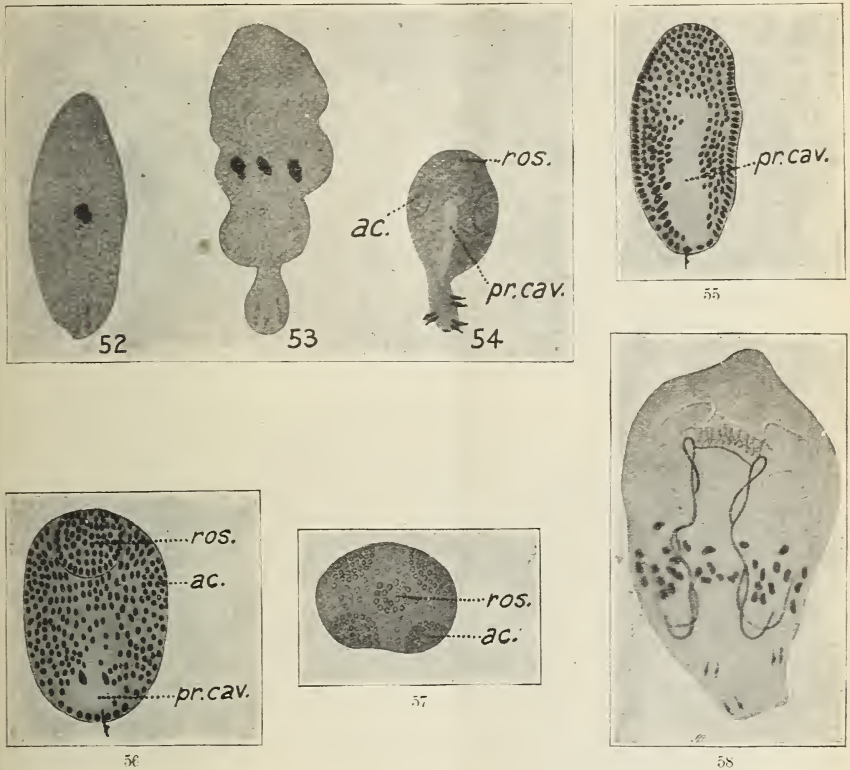
FIGS. 46-49.—*H. nana*. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, figs. 4-7, respectively.)  
 FIGS. 50, 51.—Hexacanth embryos of *H. nana*, with primary cavity: *calc.*, calcareous corpuscle; *caud.*, caudal appendage; *pr. cav.*, primary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, figs. 8, 9, respectively.)

the action of the digestive juices of the upper part of the alimentary canal seems necessary before the embryo will hatch. Consequently the eggs, as they escape from ripe segments into the intestine, do not continue developing, but pass out unchanged with the feces, and development does not proceed until they again come into the alimentary canal by way of the mouth [? or by reverse peristalsis into the stomach].

The following observations were made upon the development as it occurs in the intestinal villi of the rat (Grassi & Rovelli, 1892a). The cysticeroid, or cercocystis, to use the name employed by Villot (1882) to designate those cysticeroids which have caudal appendages, is found in a cavity, which represents the much-dilated central lymphatic cavity of the villus. Rarely there are two, ordinarily only one cercocystis in a single villus, normally so oriented that its long axis corresponds to the long axis of the villus, with its posterior end (that bearing the embryonal hooks) directed inward, i. e., toward the lumen of the intestine (fig. 67).



The *first stage* studied was that of the hexacanth embryo, as found encysted 24, 36, or 50 hours after ingestion (figs. 46–49, 52, 53), generally oval, or at times flask shaped—that is, with a body and a tail. There may be evident at this time a rather ample primary cavity which in a flask-shaped embryo is in relation with the posterior part



FIGS. 52, 53.—Hexacanth embryos of *H. nana*, without cavity, containing calcareous corpuscles. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, figs. 10, 11, respectively.)

FIG. 54.—Embryo of *H. nana* after the appearance of the primordia of rostellum and suckers: *ac.*, suckers; *pr. cav.*, primary cavity; *ros.*, rostellum. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 12.)

FIG. 55.—Longitudinal section of embryo of *H. nana*; *pr. cav.*, primary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 14.)

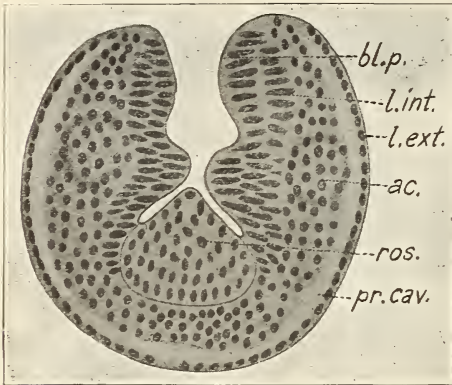
FIG. 56.—Longitudinal and slightly oblique section of embryo of *H. nana* after the appearance of primordia of rostellum and suckers: *ac.*, sucker; *ros.*, rostellum; *pr. cav.*, primary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 15.)

FIG. 57.—Embryo of *H. nana*. Same stage as preceding figure, in cross-section: *ac.*, sucker; *ros.*, rostellum. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 16.)

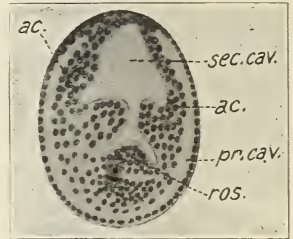
FIG. 58.—Cercocyst of *H. nana* completely developed. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 13.)

of the body, and sometimes with the tail also (figs. 50, 51). The embryonal hooks are generally found on the tail, sometimes also on the posterior part of the body, arranged in pairs. The embryos often show irregularities in form, prominences, etc. (figs. 47–49, 53). In the middle of the body there may be found one, two, or three calcare-

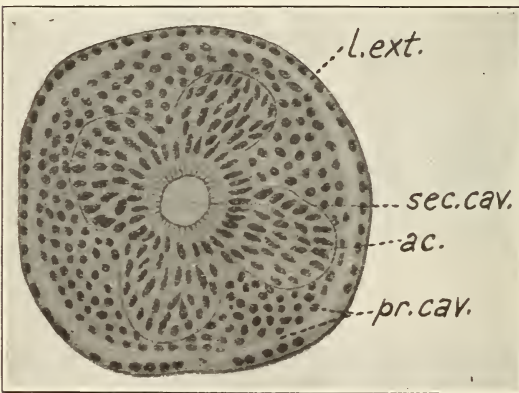
ous corpuscles. The cells making up the embryo are at this stage irregularly disposed and all very small, except a few which are in immediate relation with the tail and primary cavity (fig. 55). Neither in this nor in succeeding stages was a subcuticular muscle system observed.



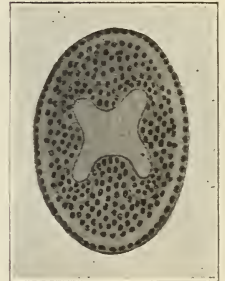
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61



60



62

FIG. 59.—Longitudinal and slightly oblique section of *H. nana* after the invagination of its anterior portion: *ac.*, sucker; *bl. p.*, anterior opening of secondary cavity; *l. ext.*, external wall; *l. int.*, internal wall; *pr. cav.*, primary cavity; *ros.*, rostellum. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 17.)

FIG. 60.—Embryo of *H. nana*. Same stage as preceding figure, in cross section at the level of the suckers: *sec. cav.*, secondary cavity. Other letters as in preceding figure. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 18.)

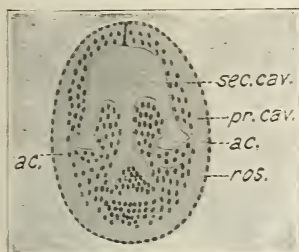
FIG. 61.—Longitudinal and slightly oblique section of an embryo of *H. nana* at a stage somewhat later than fig. 59: *ac.*, suckers; *pr. cav.*, primary cavity; *ros.*, rostellum; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 19.)

FIG. 62.—Transverse section of an embryo of *H. nana* at the same stage as preceding figure. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 20.)

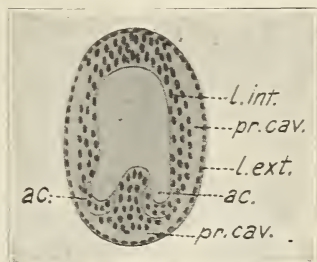
The *second stage*, as observed in the fresh state, still showed the cavity, and in the anterior part a deep, narrow, invaginated depression, shaped in longitudinal optical section like an inverted Y (fig. 54). At this stage, also, there are more or less noticeable four points in which



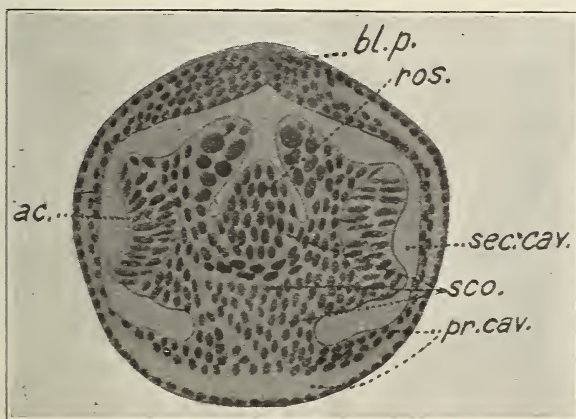
the cells are so disposed as to indicate four rounded masses. Sections of this stage (figs. 56, 57) confirm the presence of the four-rounded masses, and in the region of the Y-shaped invagination there is to be distinguished another accumulation of cells, the primordium of the rostellum. Accumulations of cells were occasionally found in other regions of the embryo similar to the four masses mentioned, but since



63



64



65

FIG. 63.—Longitudinal section of an embryo of *H. nana* at a later stage than preceding figures: *ac.*, suckers; *pr. cav.*, primary cavity; *ros.*, rostellum; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 21.)

FIG. 64.—Longitudinal section of an embryo of *H. nana* at about the same stage as the preceding figure, through a different plane: *ac.*, suckers; *l. ext.*, external wall; *l. int.*, internal wall; *pr. cav.*, primary cavity; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 22.)

FIG. 65.—Longitudinal section of an embryo of *H. nana* at a stage preceding the appearance of the definitive hooks: the rostellum is retracted; *ac.*, sucker; *bl. p.*, anterior opening of secondary cavity; *pr. cav.*, primary cavity; *ros.*, rostellum; *SCO.*, scolex; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 23.)

the latter appeared to be constant in many examples, both in the fresh state and when sectioned, the conclusion was arrived at that the four masses in question were the primordia of the suckers.

The second stage is therefore characterized by the formation of the primordia of the rostellum and suckers.

In the *third stage* (figs. 59, 60, 62) the anterior part of the body is invaginated into the posterior, and the primary cavity has become

reduced to the point of disappearance, or at most containing but very little fluid, except behind, where it is in relation with the tail, in which region it remains large and may contain cells of stellate form. The tail has not increased in length, and still bears embryonal hooks. Without meaning thereby to establish any homology, Grassi compares this stage to a gastrula. The anterior opening thus corresponds to a blastopore, the secondary cavity formed by invagination to an enterocœle, and the primary cavity lying between the outer and the inner wall to a blastocœle. The outer wall, analogous to the ectoderm of a gastrula, is very thin, consisting of an irregular layer of more or less flattened cells, and, external to this, a thin cuticula. The inner wall, analogous to the entoderm, is irregular and thick, apparently lined internally with cuticula. The rostellum preserves the shape it had in the former stage, but as a result of the invagination of the anterior part of the body now lies posterior of the plane of the suckers.

In the next following stages (figs. 61, 63, 64) the suckers have moved backward, and the anterior opening of the secondary cavity has closed over.

At later stages (figs. 65, 66), reached 40, 50, or 70 hours after ingestion, the scolex is definitely formed. It remains attached behind to the inner wall by a peduncle. A little bridge of cuticula still indicates the place where the anterior opening of the secondary cavity has been closed over. The rostellum may be seen in a state of extension. The definitive hooks have not yet appeared. The tail persists unchanged with the embryonal hooks.

In a still later stage, reached in 80 to 90 hours after ingestion, the hooks have appeared on the rostellum, and the excretory vessels become evident (fig. 58).

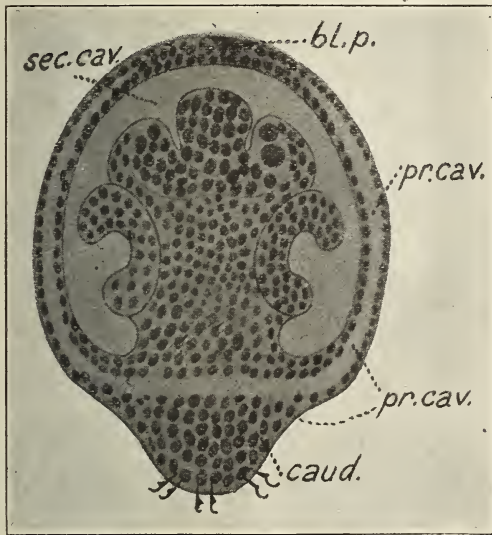
The next stage seen was that of the young tapeworm, with short neck and no trace of segmentation, attached to the epithelium of the villus.

No observations were made regarding the manner in which the cercocystis leaves its position in the villus, and becomes transformed into the adult worm.

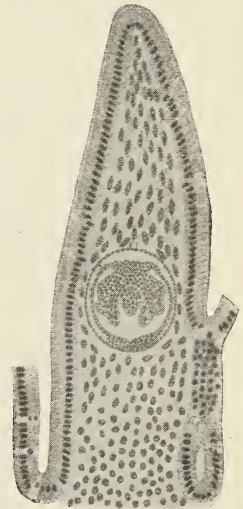
Not only was the rapidity of development found to vary in different rats, but various stages were found occurring simultaneously in the same host.

Attempts were made to infest human subjects with eggs and mature segments both from man and from rats. Experiments were made upon eight persons, but except in one case the results were negative. This case was that of a boy five years old, who, 15 days after ingesting several segments of *Hymenolepis nana* from a rat, began to pass eggs in his feces, and after the administration of an anthelmintic, expelled about 50 worms. Another instance might be mentioned here, in which a boy, who, to judge from fecal examinations, was free from

*Hymenolepis*, was found to be infected after a month, during which time he was accustomed to collect the feces of an infected patient for use in Grassi's experiments. As Grassi stated, however, these two cases are not conclusive, since the experiments were made in a country where the parasite is common, and since, also, the worms might have been present in the intestine without eggs being manifest in the feces. As further evidence of the occurrence of a development in man similar to that which occurs in the rat, Grassi (Grassi & Rovelli, 1892a) mentions cases occurring during the years 1890 and 1891 in children of well-to-do families. Some of the children belonging to these families would become infected, and, 2 to 4 months later, their



66



67

FIG. 66.—Longitudinal section of an embryo of *H. nana* at about the same stage as the preceding figure; rostellum protracted: *bl. p.*, anterior opening of secondary cavity; *caud.*, caudal appendage; *pr. cav.*, primary cavity; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 24.)

FIG. 67.—Longitudinal section of an intestinal villus of the rat, containing a cercocystis of *H. nana*. Enlarged. (After Grassi & Rovelli, 1892a, pl. 3, fig. 25.)

brothers and sisters would also show infection. In such cases it seemed to Grassi that the chances are very much against the possible swallowing of invertebrates which might contain cysticercoids, and that the circumstances are arguments in favor of the occurrence of direct infection, through the feces, from one child to another. Somewhat similar evidence is given by Venuti (1895), who, according to Massari (1898), was able to explain the phenomena associated with the appearance of *Hymenolepis* among the inmates of a boys' asylum at Catania only upon the assumption that direct infection occurred. (See p. 55.)

In the absence of conclusive positive experimental evidence, one may not, of course, make the absolute statement that *Hymenolepis nana*



develops in man after the manner determined by Grassi in the case of the rat, but it is safe to assume that a similar development occurs in both hosts, at the same time not forgetting the possibility, in both cases, that development might occur also by means of an intermediate host.

## ABSTRACTS OF CASES OF HYMENOLEPIS NANA IN MAN. <sup>a</sup>

### AFRICA.

Cairo, Egypt, 1851 ..... 1 case.

*Case No. 1.*—BILHARZ (SIEBOLD, 1852) was the first to observe *Hymenolepis nana* in man, when he found at the autopsy of an Egyptian boy who had died from meningitis a very large number of these worms, occupying a restricted portion of the ileum.

Cairo, 1885, 1892 ..... 2 cases.

*Cases Nos. 2 and 3.*—INNES (SONSINO, 1885) found a single example in the intestine of a young Nubian girl who had been drowned, and in 1892 (INNES, 1898, p. 65) encountered the parasite a second time, finding 20 specimens in the intestines of an adult, who had died from anemia. The mucous membrane of the ileum showed 5 or 6 little bloody extravasations like flea bites, and quite different from the wounds produced by *Agchylostoma* (not reported present in this case), but whether due to the tapeworms the author could not say, since the parasites were no longer adherent.

### EUROPE.

Nottingham, England, 1854–1855 ..... 1 case.

*Case No. 4.*—W. H. RANSOM (1856, pp. 598–599) in July, 1854, found the eggs of *Hymenolepis nana* in the feces of a little girl. Their identity, however, was not recognized until more than thirty years later (GRASSI & CALANDRUCCIO, 1887a, p. 285; RANSOM, 1888, pp. 109–110.) The girl was 9 years old, of poor parents, and lived in a low, damp locality; had always been delicate, but never seriously ill; was fond of fruit and vegetables, especially raw cabbage. In March, 1854, she began to complain of feeling faint and weak in the morning; she was treated for worms by a druggist, but without result; became gradually weaker, losing flesh, strength, and color; her appetite was capricious, but not ravenous; she suffered occasionally from a pain in the left side. The ordinary symptoms of helminthiasis (such as vomiting and nausea, convulsions, and itching of seat and nostrils; ravenous appetite and gnawing pains in the abdomen; round worms, seat worms, or tapeworm joints in the stools) were all absent. Besides the eggs of *H. nana* the feces contained eggs of the whipworm, *Trichuris trichiura*. Fecal examinations of her four brothers and sisters showed them free from intestinal parasites. In the course of the following year the patient was placed under anthelmintic treatment several times; a specimen or two of eelworms (*Ascaris lumbricoides*) and pinworms (*Oxyuris vermicularis*) were passed, but if any tapeworms were expelled they passed unperceived. With careful diet and tonics her condition was much improved, although the eggs of the tapeworm were found in the feces at each examination and were still present in September, 1855, fifteen months after the case first came under observation.

<sup>a</sup>The cases abstracted have been numbered seriatim for convenience of reference, after arrangement chronologically by countries.

For additional cases see footnote, p. 7.



Milan, Italy, 1879 ..... 1 case.

*Case No. 5.*—GRASSI (1879h, p. 156) reports a case from the Milan Hospital of a girl  $4\frac{1}{2}$  years old, suffering from severe nervous troubles with epileptiform attacks, the symptoms resembling those of a basilar cerebral tumor. The child was also troubled by an intermittent diarrhea. In her feces, besides the eggs of *Ascaris*, *Trichuris*, and *Oxyuris*, were some cestode eggs determined several years later (GRASSI, 1886a, b) as belonging to *Hymenolepis nana*. Koussou and kamala were administered with negative results.

Belgrade, Servia, 1885 ..... 1 case.

*Case No. 6.*—BLANCHARD (1886e) reported the next case of *Hymenolepis* in Europe. A 7-year-old girl of poor parents came under the care of Doctor Holez of Belgrade, suffering from digestive troubles. Tapeworm was suspected and male fern administered. A *Tania solium*, some *Oxyuris vermicularis*, and 50 *Hymenolepis nana* were passed. The treatment was repeated four or five times, about 50 examples of *H. nana* being passed each time, so that altogether about 250 were expelled. This case was also reported by LEUCKART (1886a, pp. 995-997).

Lombardy and Sicily, Italy, 1886 ..... 2 cases.

*Cases Nos. 7 and 8.*—In 1886 two cases of *Hymenolepis nana* were observed at Milan by GRASSI (1886a, b, 1887d.) Two young Sicilians, one of whom seems to have been a medical student from near Catania, Sicily (CALANDRUCCIO, 1890a, p. 124), both of robust constitution, were affected with severe nervous troubles, indolence, epileptic attacks without loss of consciousness, weakening of the mental faculties, melancholia, and bulimia, which resisted all treatment, the symptoms generally resembling those exhibited by the little Milanese girl in 1879 (see case No. 5). Upon the discovery of cestode eggs in the feces male fern was administered, after ineffective trials with koussou and kamala, and each patient expelled several thousand specimens of *Hymenolepis nana*. Following this treatment all the morbid symptoms disappeared.

Cusago, near Milan, Italy, 1886 ..... 1 case.

*Case No. 9.*—This case was reported by VISCONTI & SEGRÉ (1886.) On October 9, 1886, a peasant, aged 17, in a state of extreme prostration, with severe dyspnea, entered the hospital at Milan from Cusago. Toward evening the dyspnea increased, and when the patient was seen the next morning he was unconscious, respiration stertorous, lips blue, extremities cold, and pulse thready. Death supervened shortly.

Upon inquiry it was found that for three years the patient had suffered from an habitual diarrhea, passing several yellowish stools a day. He complained constantly of colicky pains in the abdomen, which often became very severe. His appetite however, remained good, and was not perverted. He had had malaria, from which recovery was complete. He suffered from frequent headaches of short duration; always felt cold; the last two months of his life had a slight fever evenings, upon which quinine had no effect; his respiration was noisy, and light attacks of dyspnea were of occasional occurrence. Three days before entering the hospital he was seized with a violent attack of dyspnea, and repeated attacks of clonic convulsions, almost epileptic in character, each lasting for some time and followed by evacuations from the bowel.

The autopsy revealed 4 specimens of *Agchylostoma duodenale* in the duodenum, and 6 *Ascaris lumbricoides* and about 400 *Hymenolepis nana* in the ileum. The tapeworms, not adherent, were scattered through the ileum from its beginning to about 20 cm. from the ileo-cecal valve. (For pathology of this case see p. 68.)

Lombardy, Italy, 1886-1887 ..... 3 cases.

Catania, Sicily, 1886-1889 ..... 23 cases.

Italy, 1890-1891 ..... several cases.

*Cases Nos. 10 to 15.*—GRASSI (1887d) records 6 new cases, 3 observed by him in Lombardy, and 3 by CALANDRUCCIO in Catania, Sicily. In 5 of the cases the parasites were few, and only slight nervous troubles were present. In the other (No. 12), however (one of the cases of Lombardy), the nervous troubles were very marked. An autopsy was performed on one of the cases in Catania (No. 15), which showed that the worms had bored deeply into the mucosa and provoked very considerable alterations, of which, however, no account is given.

*Cases Nos. 13 to 35.*—CALANDRUCCIO (1890a) reports for Catania 23 cases in all, 3 of which he states were observed by GRASSI. It is possible that the 2 cases of the young Sicilians (7, 8) reported by GRASSI (1886 a, b, 1887d) are to be included in this number, but there seems to be some confusion in the reports of these two authors as to the identity of the various cases and a certain lack of definiteness, so that it is not possible to state the figures with accuracy.

The persons examined were mostly young and of the male sex; 21 cases were children, 2 adults; 14 at least were males, and 3 females, very likely the other 6 were males. In the feces of 20 children, aged 8 to 10 years and attending the same rural school in Catania, the eggs of *Hymenolepis nana* were found 3 times; together with the eggs of *Ascaris*, *Oxyuris*, and *Trichuris*. Of 50 boys, aged 7 to 10 years, in the Ospizio di beneficenza of Catania, 4 harbored the parasite.

*Case No. 32.*—CALANDRUCCIO observed the case of a young child, who suffered from severe intestinal troubles, which ceased two days after the expulsion of a great number of *Hymenolepis nana*.

*Cases Nos. 33 and 34.*—He also mentions in some detail 2 cases, adults who harbored numerous specimens. They suffered with alternating diarrhea and constipation, not infrequently with abdominal pains, and with more or less severe epileptic attacks of frequent occurrence. After the elimination of the parasites, the patients experienced no disturbances for several months. The symptoms later reappeared, but were less intense and less frequent. The feces were reexamined on a number of occasions, but no eggs of *Hymenolepis nana* could be found. This circumstance made it seem very probable, according to CALANDRUCCIO, that the two individuals were inherently epileptic and the effect of the tapeworms had been that of aggravating the symptoms and rendering them more intense and more frequent.

*Case No. 35.*—The case of a female child, 4 years old, is referred to by GRASSI & CALANDRUCCIO (1887a). Although this patient harbored thousands of *Hymenolepis*, she showed no symptoms except occasional abdominal pains of transitory nature.

GRASSI (GRASSI & ROVELLI, 1892a) speaks of several cases occurring during 1890–1891 among children of well-to-do families, but gives no detailed account of them.

**Varese, Italy, 1884–1886** ..... 2 cases.

*Case No. 36.*—COMINI (1887 a, d, 1888 a) reports a case of *Hymenolepis nana* in a boy, 9 years of age, born and living in Gavirate. The parents of the patient were healthy, but a paternal aunt had died with symptoms of insanity. At 14 months of age he had been treated with santonin for worms; after taking the drug his skin became cold, the lips and face blue, eyes staring, and body stiffened. After recovering from the immediate effects of the santonin he was left with a slight paresis of the extremities of the right side; this symptom, however, disappeared in a month without leaving any traces. He passed a great number of *Oxyuris* in June, 1884, after treatment with an anthelmintic clyster. On July 4 the boy was seen to become suddenly pale and comatose. After a few minutes the condition of coma was succeeded by violent clonic contractions, trismus, and foaming at the mouth. This convulsive attack lasted about two hours, and was followed again by coma of several hours' duration.

On the 25th of August there were a couple of attacks of an epileptic nature, which up to the 14th of September were of daily occurrence, sometimes as many as 6 in twenty-four hours. After this the attacks ceased.

In July, 1886, nearly two years later, there was a recurrence of the nervous symptoms. Eggs of *Hymenolepis nana* were found in the feces. Up till October the child suffered with severe cerebral troubles and epileptiform attacks. The eggs were still abundant in the feces. Extract of male fern was prescribed. Although the worms were not found in the stools after the treatment, the eggs disappeared from the feces, and the attacks ceased. In the latter part of December (COMINI, 1887a, p. 61) the attacks again recurred more severe than before, and the eggs likewise had reappeared in the feces. COMINI (1888a) is rather doubtful as to the etiological importance of *Hymenolepis* in this case, in which there was already an apparent congenital predisposition to nervous disease.

*Case No. 37.*—A second case was observed December, 1886, by COMINI (1887 a, d, 1888a) at the hospital in Varese.

The patient, a little girl of 3 years, with a tuberculous mother, had suffered for two years with a continual dyspnea, without fever or cough, but often accompanied by pains in the abdomen, and functional gastro-intestinal disorders. Eggs of *Hymenolepis nana* were numerous in the feces (7 to 8 in every preparation). Eggs of *Ascaris* were also present.

After anthelmintic treatment the dyspnea became gradually better and disappeared entirely in a few days. A year later the child was in excellent physical condition, and the feces were free from eggs of *Hymenolepis*.

**Pavia, Italy, 1886–1889** ..... 6 cases.

These 6 cases were observed in very complete detail by SENNA (1889) at the clinic of Professor ORSI, who also published a short paper (ORSI, 1889) in regard to them.

*Case No. 38* (SENNA'S Case I).—Epileptiform convulsions with intestinal helminthiasis.

Female, 15 years of age, domestic. Always weak and of a delicate constitution, she had suffered for three years from convulsive clonic attacks, with foaming at the mouth and complete loss of consciousness. These attacks were at first fleeting and occurred only at long intervals, but as time went on became more frequent and insistent, especially at night. There were present also gastric dyspepsia and troublesome abdominal paresthesia, with a sense of constriction in the fauces. Anthelmintics had been tried with no apparent result. She had also had at one time a convulsive cough which lasted a year, a suppurating keratitis of the right eye, and frequent inflammation of the cervical glands. Her father and brother were both healthy, but the former, a day laborer, was somewhat given to drunkenness. Neither nervous maladies nor pellagra was known in the family; a paternal uncle had died of consumption.

The patient entered the clinic the last of November, 1886. The convulsive attacks continued, occurring almost every night, and rarely in the daytime. Some nights the attacks were very transitory and passed almost unperceived by the nurse. The girl was somewhat melancholy, taciturn, and preferred solitude. She was, however, of good intelligence, and careful physical examination revealed no morbid organic conditions of importance. Examination of the feces showed numerous eggs of eelworms (*Ascaris lumbricoides*), a very few of hookworms (*Ancylostoma duodenale*), a few of whipworms (*Trichuris trichiura*), and of *Hymenolepis nana*. Several eelworms were passed after the administration of santonin, but no tapeworms were seen, nor were any of the latter perceived in the stools after treatment with ethereal extract of male fern. Some tapeworms, however, were undoubtedly expelled, since the eggs were no longer to be found in the feces. The patient improved, and left the hospital the latter part of December.

Amelioration lasted only a few months; the convulsions came on again, and the patient returned to the hospital in April, 1888. As before, she suffered with epilepti-



form convulsions almost every night, more rarely by day, often accompanied by involuntary micturition; there were occasional manifestations of somnambulism. She was more taciturn than before, and somewhat stupid. Eggs of *Ascaris* and *Hymenolepis* were again found in the feces. Male fern was administered, but no worms were obtained. The patient, after a month, left the hospital.

She returned a third time in the middle of April, 1889. For some time after leaving the hospital she had been fairly well, but more recently the convulsions had reappeared, and occurred almost every night. She had menstruated for the first time in August, 1888; afterwards only in October, and again in February. The girl is still more melancholy and self-centered than before, does not wish to associate with any one, is restless, inclined to lament over everything, and is very slow and unwilling in answering questions. Physically she is fairly well developed, but is somewhat pale and languid. There are evident scrofulous signs—a peculiar softness of the skin, tumid lips, scar on the right eyeball from keratitis, sinistral cervical adenitis. The head is of normal size and shape, intelligence good, no defects in the special senses, appetite and thirst moderate, tongue coated, breath fetid, digestion difficult, defecation and uropoietic functions more or less regular, a rough diffuse vesicular murmur in the chest, no cough nor dyspnea. Patient complains of a troublesome abdominal paresthesia, a sensation as of a snake crawling through the abdomen and up to the fauces, with a sense of heat in the epigastrium, and strangulation at the throat. This sensation is often more intense before the daily convulsive attack. The pulse is regular, urine normal, and there is no fever. In the feces are eggs of *Ascaris*, *Trichuris*, and a few of *Hymenolepis nana* (1 to 2 per slide).

After entering the hospital the patient had one convulsive attack during the daytime. She fell suddenly, with diffuse clonic spasms, foamed at the mouth, and was entirely unconscious. When seen by Senna she was in a comatose condition, not responsive to command nor reacting to cutaneous stimuli; the pupil was not abnormally dilated and reacted a little to light. Another day she was observed during an attack of diffuse tremor, which she said was of frequent occurrence. Almost every night she was taken with fleeting convulsive attacks, moved arms and head, foamed at the mouth, and uttered a groan or a whistling sound. In the morning she had no recollection of the occurrence.

Five grams ethereal extract of male fern, followed by a purgative, were administered. In the copious watery stools no tapeworms could be found, but for several days following the patient was much improved, no longer felt the peculiar sensations in the epigastrium and throat, and was not troubled with the muscular spasms. The eggs of the tapeworm were absent from the feces. After a short time light convulsive attacks during the night again appeared, but the patient felt so much improved that she left the hospital toward the end of the month.

It is evidently not possible in this case to establish an absolute connection between the epileptic attacks and the presence of *Hymenolepis nana*, since a complete and lasting cure was not attained, and since the patient was scrofulous, debilitated, and the child of an alcoholic father. It is certain, however, that she improved after each treatment, and it is justifiable to consider, Senna thinks, that the presence of *Hymenolepis nana*, and perhaps also of the other intestinal worms, if not the sole cause, at least had great influence upon the epileptiform manifestations, since they reappeared or became less frequent in correspondence with the presence or absence of eggs in the feces.

*Case No. 39* (Senna's Case II).—Epileptiform convulsions, with intestinal helminthiasis (*Hymenolepis nana*).

School girl, 16 years old, native of Stradella, Lombardy. Mother died in childbirth; three brothers and one sister dead; causes not known. One brother living; healthy. Father living; inebriate.

The patient had always been in the best of health until the year before, when she



had an attack of typhoid fever. She menstruated for the first time in December, 1887, and since then only in the middle of March. Had worked for four years at Milan as a weaver; came to Pavia in October, 1887, to live with her grandmother and attend school. Two months before entering the hospital she began to suffer with severe headaches, especially while working, and after eating; she also noted an increase of appetite, and a slight cardiac palpitation on muscular effort. Digestion and bowels remained regular. About a month after the beginning of these symptoms, the patient was rudely accosted by some soldiers. She was not much frightened at the time, but on reaching home she was taken with a convulsive attack. From this time similar attacks were experienced nearly every day, frequently two or three times. She would be found on the ground, unconscious, with a bloody froth at the mouth, and biting her tongue. Together with these symptoms there was an acute pain in the epigastrium, a sense of constriction in the fauces, and frequently after the attacks, diplopia.

The patient came to the hospital the middle of March, 1888. She was physically well developed, somewhat pale, the gait was normal, decubitus indifferent, intelligence good, character mild and tranquil, no alteration in the special senses, nor in the sensibility and mobility of the face and cervical muscles. The eyes appear somewhat salient, react regularly to light, movements of the bulb intact, except occasional diplopia from insufficiency of the right rectus internus. Tongue normal in size, form, and direction, with a number of shallow furrows in the mucosa of the anterior two-thirds, irregularly disposed and filled with a whitish scum. There is increased appetite without malacia or pica, thirst moderate, speech and deglutition normal. There are no abnormalities of neck or chest. The form and volume of the abdomen; gastric, intestinal, uropoietic and menstrual functions; pulse, urine; the motility, sensibility, and reflexes of the extremities are all normal. Complete apyrexia. The feces contain eggs of *Ascaris*, *Trichuris*, very few of *Agchylostoma duodenale*, and a great many of *Hymenolepis nana*, 7 to 8 or more in every preparation. Besides the severe headache, the patient complains of a painful sensation of strangling, which is almost continuous, often more intense just before the onset of a convulsive attack, and of a persistent pain in the epigastrium, exacerbating on palpation. The last sensation is often that of a severe gnawing.

At the beginning of her stay at the hospital she had a convulsion nearly every day, and sometimes two or three. The onset of the attack is usually sudden, sometimes preceded by an intense pharyngeal spasm. During severe attacks consciousness is entirely lost. The patient falls with a groan, the face is pale with an astonished expression, eyes fixed and expressionless, with a slight mydriasis. The superior extremities, especially the right, are shaken with coarse, irregular, clonic movements, the trunk is bent to one side, frequently the left, and the lower extremities exhibit diffuse clonic spasms with vibrations finer and more rapid than those of the upper.

The pupils are not affected by light; there are no losses of urine or feces; sometimes there is a slight foaming at the mouth. After a few seconds the patient gives signs of regaining consciousness, but for some minutes the face retains its look of astonishment and the eyes their expressionless stare. After the convulsive attack she complains for several hours of headache and remains somewhat depressed; does not recall having had the attack.

After treatment no worms were found in the feces, but the eggs were afterwards absent. The abdominal pains and the pharyngeal spasm disappeared and the epileptiform attacks were much diminished in frequency. Eggs having again been found in the feces, treatment was repeated, and the attacks ceased entirely for fifteen days. At the end of this time they returned, but much less intense than at first, and the girl left the hospital, uncured, in June, 1888.

More recently Senna saw the patient, who told him that she suffered from the con-

vulsions for four months after leaving the hospital, but they then disappeared and had not since returned. She felt entirely well and appeared happy and in the best of health.

*Case No. 40 (Senna's Case III).—Sinistral hemiparesia and other diffuse nervous disturbances (from *Hymenolepis nana*?).*

School girl, 11 years old, from Sanazzaro. Family history good. According to her mother, child was always bright, vivacious, and of a sweet and affectionate disposition.

In the beginning of February, 1889, it was noticed that the girl, when standing or walking, swayed upon her legs as if to fall. When talking, the angle of her mouth was drawn toward the right side. She complained of slight headaches, and occasional vertigo; fell to the ground one day while going to school. The appetite and digestion remained good, there was no fever, no vomiting, no spasms of any sort, and the child continued to go to school with no appreciable change in character or intelligence. Little by little walking became more difficult, the left arm and leg became weakened, and there was often diplopia.

The patient entered the hospital the 18th of February, 1889. She is well developed for her age; of healthy color. Gait is uncertain and vacillating, and left leg drags. The eyes are fixed, and she carries the head inclined toward the left shoulder with the chin turned to the right. Closing the eyes has no effect on the gait. The decubitus is indifferent, patient is calm, and the sleep tranquil. Form and size of head is normal. There is considerable deficiency in the action of the muscles on the left side of the head. Special senses are normal; pupils somewhat dilated, normal in reflexes and accommodation. Moderate degree of convergent strabismus, the movement of the right eye outward being deficient; occasionally there is a slight nystagmus; the patient no longer complains of diplopia. Epiphora of the left eye, lachrymal duct open; anesthesia of cornea and conjunctiva. No objective change in the sensibility of the face, no tender spots. Tongue and uvula deviate to the right. Appetite is good, thirst moderate. Phonation, mastication, and deglutition normal; no abnormal sensation at the throat, no painful spots nor spasms in the neck. No pains nor abnormal sensations in chest or abdomen; digestion and other functions regular. Examination of the spinal column negative; attitude of extremities normal; no change in sensation, no muscular spasms. Weakness of the extremities of the left side. Painful sensation of tingling and formication on the left side of the body (excepting the face). Electro-muscular contractility same on both sides; the cutaneous and tendinous reflexes are regular, with the left patellar reflex a little more conspicuous than the right. Urine and pulse are normal. No fever. Eggs of *Hymenolepis nana* present in the feces to the number of 5 or more in every preparation. After the administration of 3 grams of ethereal extract of male fern an extraordinary number of the tapeworms were passed.

In diagnosing this case Orsi excluded cerebral tumor on account of the rather rapid rise of the morbose phenomena, unaccompanied with much pain, partial or general spasms, or vomiting. Tubercular meningitis was excluded by the lack of tubercular or scrofulous antecedents, and the absence of febrile symptoms and of abdominal or thoracic tuberculosis. The symptoms were similar to those of a cerebral hemorrhage with multiple foci, but the age of the patient rendered this diagnosis very doubtful. Senna remarks upon the possibility of a reflex paralysis from irritation caused by the parasite.

After the elimination of the worms the patient became no better, although her feces no longer contained eggs. She left the hospital the 8th of March, continued to grow worse, without the reappearance of eggs in the feces, and returned again to the hospital in the early part of April. She was still intelligent, but appeared to be dazed and could speak only with great difficulty. The sinistral hemiparesia was more marked, and the right leg had become weakened. The other symptoms were

as before. Male fern was administered without results. The patient died a few weeks later, in the early part of June, 1889, after suffering for three or four days with a violent headache, especially on the right side, and a high fever. No autopsy was made.

*Case No. 41 (Senna's Case IV).*—Complete paralysis of the right external oculomotor, and corresponding facial paresis, with *Hymenolepis nana*.

Female, 7 years old, daughter of a fruit vendor, from Borgorato Mormorolo (Voghera). Family history good; no preceding illness of any importance. In September, 1888, the patient began to show a weakness in the extremities of the right side; gait became irregular; the mouth was drawn to the left; when she held anything in her hands clonic convulsions of the right arm were often observed. Toward the middle of February, 1889, diplopia and convergent strabismus, affecting the right eye, appeared. Shortly after this she began to have slight headaches at intervals; her intelligence remained good but speech became difficult. An anthelmintic was administered; the general state of her health was improved, but the strabismus persisted.

The patient on examination appeared well developed, and of healthy color. She walked very well, but exhibited a little uncertainty in rapid movements, and held the head slightly inclined toward the right shoulder. She no longer complained of weakness of the right arm and leg, nor of headache. She was quite intelligent, the size and form of the head were normal, there was no objective change in the sensibility of the face, senses normal, no tender spots nor spasms. There was apparently complete paralysis of the right rectus externus, the eye could be moved upward or downward, but lateral movement was impossible. Diplopia was present. The pupils were regular and reacted well to light. The left angle of the mouth was drawn upward and outward. The appetite was good; thirst moderate; the tongue normal, deglutition good; speech difficult, but according to the patient, improved somewhat compared with its former condition. There was an occasional dry cough, somewhat spasmodic; now and then a deep sigh. Neck, chest, and abdomen normal. No pains nor paresthesia in abdomen.

The gastro-intestinal and uropoietic functions were regular. There were no objective evidences of diminished power of the limbs, and hyperkinetic manifestations and alterations of sensibility were absent; reflexes persistent. Urine and pulse regular. No fever. The feces contained the eggs of *Hymenolepis nana* and *Ascaris lumbricoides* in moderate numbers. Three grams of ethereal extract of male fern followed by a purgative were administered and a large number of *H. nana* were expelled. The speech and gait were much improved in a few days, although the strabismus and deviation of the mouth continued. The strabismus finally showed signs of amelioration, and the right eye could be moved outward to a barely perceptible degree. The eggs were no longer present in the feces.

*Case No. 42 (Senna's Case V).*—Chronic chorea minor caused by *Hymenolepis nana*.

Boy, 11 years old, peasant, from Cervesina. Family history good. Operated upon when a baby for vesicular calculus; has had malaria; and several times intestinal helminthiasis, with violent colic, without reflex nervous phenomena; cured after the expulsion of ascarids with santonin.

In January, 1889, the patient began to experience a difficulty in talking and in moving his tongue. Some days later he was affected with convulsive movements of the head and face, then of the arms. Afterwards the trunk and lower extremities became similarly affected. His condition continued to grow worse, and he entered the hospital in the latter part of April.

The patient is tolerably well developed, with fine skin and rather pallid mucous membranes. Irregular, clonic, involuntary muscular contractions occur continually, sometimes involving the entire body, which render the erect posture and the gait uncertain and vacillating. In brief, the symptoms are those common to chorea minor. Everything that excites or stimulates the patient aggravates the muscular



agitation, which can not be controlled in the least by the will. The sleep is tranquil, and nocturnal muscular spasms are absent. He is intelligent; the speech, however, is incoherent, monosyllabic, and at times almost incomprehensible. The pupils are unequal, sometimes one, sometimes the other being the larger, but they react well to light. Vision is diminished in the left eye, there is diplopia, and unilateral convergent strabismus, due to insufficiency of the left rectus externus. Special senses and sensibility of the face are normal. Appetite and digestion are good. Apex beat of heart in fourth intercostal space in the nipple line, and heart of normal size. The systole is accompanied by a slight blowing murmur at base and apex. Size of liver normal. Spleen very slightly enlarged. There is pain and a sense of pressure in the epigastric and umbilical regions. The abdomen is regular in form and volume. The gastro-intestinal and uropoietic functions are normal. Examination of the spinal column resulted negatively. Excepting the choreic movements, the nervous system showed no abnormalities in the trunk and extremities. The pulse and urine are normal and there is no fever. In the feces are eggs of *Trichuris*, *Ascaris*, and *H. nana* (2 to 4 per slide).

The administration of 4 grams of extract of male fern was followed by the evacuation of about 50 tapeworms. The next day the patient was in a state of prostration, with severe pains in the abdomen. The following day he was resting much easier; after that improved rapidly and was soon entirely well. Eggs of *Hymenolepis nana* were no longer to be found in the feces.

*Case No. 43* (Senna's Case VI).—School girl, 11 years old, from Sommo. Family history good, and patient had always been in good health.

In January, 1888, the patient became taciturn and seemed stupid; weakness and irregular clonic spasms appeared in the extremities of the right side, and after a short time the speech was affected and became difficult. There was diplopia; the mouth was drawn upward on the right side; there were also headache, pharyngeal spasms, paresthesia and pains in the abdomen, but functional troubles were absent. The symptoms became worse, and by Fall the spasms had begun to affect the left side, but with less intensity. Anthelmintic powders containing santonin were administered repeatedly without result. In December a teniafuge of unknown composition was given, and the patient became much better, so that by the end of a month she was entirely well. After three months, however—in March, 1889—the symptoms suddenly reappeared, but less intense and more intermittent. The child was brought to the hospital in May.

The patient is rather slender, with fine pale skin. She is reserved and taciturn, has some difficulty in moving the extremities of the left side, has headache, and paresthesia and pain in the abdomen, with crawling and gnawing sensations. She also experiences a feeling of constriction at the throat, and sometimes diplopia. Objective examination reveals nothing noteworthy except a slight diminution in the muscular strength of the left arm, possibly also of the leg. Clonic muscular movements, limited to the left hand and forearm, appear at long intervals. The eggs of the *H. nana* are present in the feces. Extract of male fern was administered, and, although no worms were seen in the stools, all the symptoms disappeared very shortly.

**Piedmont, Italy, 1886-1887**.....1 case.

*Case No. 44*.—At a meeting of the Academy of Medicine of Turin, PERRONCITO (1887) reported the first occurrence of a case of *Hymenolepis nana* in Piedmont, communicated by Doctor Airoldi, and later (1891) gave a fuller account.

The patient was a male, 19 years old, peasant, of robust constitution, and up to the age of 14 or 15 had not been ill, with the exception of an occasional abdominal pain during childhood. He had a doubtful case of typhoid fever, lasting a week, in the Fall of 1885.



At the time of examination, January, 1887, the patient complained of headache, sense of fatigue in the lower limbs, numbness in the lumbar region, and malaise, more pronounced after the least exertion. Slight pains in the joints were attributed to the irregular life which the boy had led between the age of 13 and 15, when he wandered about in the fields in all sorts of weather, hunting for birds. For two years he had experienced frequent attacks of vertigo, and losses of consciousness lasting about a minute. The physical examination showed no abnormalities. The feces contained numerous eggs of *Hymenolepis nana*.

After treatment the patient passed a large number of worms, and the symptoms rapidly subsided. In December, 1888, he was in perfect health, and more recently, according to his father, was still entirely well, with no return of his former trouble.

**Sommariva del Bosco, near Turin, Italy, 1887-1888** ..... 1 case.

*Case No. 45.*—PERRONCITO & AIROLDI (1888 a, b, c) report the case of a boy of 6 years. Two years before he came under observation he had suffered from an attack of typhoid fever at Turin, and during convalescence was sent to the country and placed on a raw-meat diet. Soon afterwards he began to pass segments of *Tænia saginata*. He also suffered from headache, abdominal pain, lack of appetite, and frequent vomiting, the symptoms altogether indicative of gastro-enteric and nervous disturbances due to helminthiasis. The case was seen for the first time in November, 1887, when the feces were found to contain eggs of *Tænia saginata* and large numbers of the eggs of *Hymenolepis nana*. A dose of 4 grams of ethereal extract of male fern was administered, most of which was vomited; a number of pieces, however, of *Tænia saginata* and about 1,000 *Hymenolepis nana* were passed.

On May 24, 1888, the case was again examined. According to his parents the boy was often ill, with frequent pains in head and abdomen, lacked appetite, and vomited frequently. The patient appeared rather more pale than at the former examination. The stools, as before, contained eggs of *Hymenolepis nana* and of *Tænia saginata*. A purge was given the 24th, and several pieces of *T. saginata* were passed. The next day the boy was placed on special diet, and another purgative administered that evening. On the morning of the 26th he was given 6 grams of ethereal extract of male fern, and in an hour and a quarter afterwards 15 grams of castor oil. (Some of the male fern was vomited three-quarters of an hour after administration). At about noon the evacuations began; a *Tænia saginata* about 4.5 meters long and more than 1,000 *Hymenolepis nana* were passed.

**Tuscany, Italy, 1889-1895** ..... 5 cases.

SONSINO (1889, 1891, 1895a) has reported 5 cases of *Hymenolepis nana* from the neighborhood of Pisa.

*Case No. 46.*—In October, 1889, the feces of a 9-year-old girl from the Comune di Cascina, who had been suspected of uncinariasis, were sent to Sonsino for examination. Eggs of *Hymenolepis*, but none of *Agchylostoma*, were found. The girl died shortly afterwards of a febrile malady (SONSINO, 1889, 1891).

*Case No. 47.*—The second case (SONSINO, 1889, 1891), which was that of a man from Pisa, likewise suspected of uncinariasis, was seen in the same month. Ethereal extract of male fern gave no apparent results. The man was afterwards treated with thymol, some *Agchylostoma* were passed, but he continued to suffer from gastro-enteric troubles. As late as April, 1890, his feces still contained eggs of *Hymenolepis*, but less in number than at first. This patient was again examined five years later (Sonsino, 1895), and eggs of *Agchylostoma*, evidently from a new infection, were found in large numbers, but none at all of *Hymenolepis nana*.

*Case No. 48.*—A 7-year-old girl from a family of brickmakers of the same locality as that of the first case (Comune di Cascina) was brought in April, 1891, to Sonsino (1891, 1895a), to be treated for possible uncinariasis. The parents of the child were strong and healthy; during the first two years of her life the child herself was per-

fectly well, but after that began exhibiting evidences of a perverted appetite, and would eat mud, plaster, charcoal, and even feces of animals. Her health suffered and she grew pale. At about the age of 6, consequent upon a change of habitation to a spot where she no longer had so many opportunities of satisfying her depraved appetite, and where she could be watched more closely, she was cured of the habit. Her physical condition did not improve, however, and she continued to be subject to fatigue, cardiac palpitations, and dyspnea. Her appetite was, if anything, greater than normal, and she suffered from frequent indigestion.

On examination the patient appeared somewhat cachectic, due rather to the waxy appearance of the skin than to any actual emaciation. The lungs, heart, liver, spleen, and kidneys were normal; the abdomen was not painful on palpation, but digestion was difficult, with frequent acid eructations. The patient often complained of transient pains in the body and limbs. The cervical glands were slightly enlarged and the voice was rather hoarse. Fecal examinations showed neither eggs of *Agchylostoma* nor of *Oxyuris*. Occasional eggs of *Trichuris* and some of *Ascaris*, and one or two per slide of *Hymenolepis nana* were found. Treatment with santonin and castor oil expelled several *Oxyuris*. The next morning after this treatment extract of male fern and calomel were administered. In the first three of the five stools which followed during the day, *Oxyuris* and more than 100 *H. nana* were passed, while in the last two only *Oxyuris* were expelled.

Notwithstanding the apparent success of the treatment the patient became no better. Eggs of *Hymenolepis* were no longer present in the feces, but *Ascaris* and *Trichuris* eggs were still to be found. Treatment was again instituted, and *Oxyuris* and *Ascaris* were passed, but neither *Hymenolepis* nor *Trichuris*.

Several months later, in November, 1891, SONSINO (1895a) again examined the feces of this patient, and found the eggs of *Hymenolepis* more numerous than before. Electuaries of male fern and calomel were administered twice and vomited each time. The second time some of the dose undoubtedly took effect, as about 250 *H. nana* in fragments were expelled. A third dose a few days later expelled about 15 *H. nana*, and a large number of *Oxyuris*.

In January, 1894, the feces were free from *Hymenolepis* eggs, but contained those of *Ascaris*, *Trichuris*, and *Agchylostoma*. After two treatments with santonin and thymol a couple of male *Agchylostoma* were expelled.

Finally, in May, 1895, the feces were free from eggs of parasites, except a few of *Trichuris*, and the patient was in a state of comparative health, considering her scrofulous constitution.

*Case No. 49.*—The fourth case (SONSINO, 1895a), first observed in October, 1892, was a boy, 23 months old, from a family of brickmakers of the same locality as that of the first and third cases. Seven members of the family had had uncinariasis. The child's feces contained large numbers of *Hymenolepis* eggs, but none of any other parasite. Until the age of 8 months, mother's milk had been his only food, and up to that time he remained perfectly well. He then began to eat other food also, and likewise to suffer from lenteric diarrhea, with frequent vomiting and motor disorders, such as shivering, biting the lips, gritting the teeth, strabismus, and an almost continuous automatic lateral movement of the head of the nature of a clonic partial spasm (*spasmus nutans*), referable to a lesion or functional disorder of the spinal accessory nerve. The boy was weaned entirely and his symptoms gradually became worse.

When seen by SONSINO the patient exhibited the motor disorders noted above, complained also of pains in the abdomen and head; his nose itched very often, and he was suffering from an intense intestinal catarrh. The abdomen was flatulent, but not sensitive to pressure. There was some fever, and the patient was inclined to be drowsy.

On October 27, after treatment with male fern suspended in mucilage, and calo-

mel, about 1,000 *H. nana* were passed. The next day the boy had improved, the fever had subsided, and the intestinal and motor troubles showed signs of diminishing.

When seen on December 11, the patient had gained flesh and color, but the diarrhea had returned. *Hymenolepis* eggs were again present in the feces. On December 19, male fern was administered and over 120 worms were passed.

On January 22, 1893, eggs were again found, and after another dose of male fern, from a portion of the evacuations following 200 worms were collected.

Three months later the boy was feeling fairly well. He had no diarrhea, and slept well, but there was still some lateral movement of the head. Eggs were found in the feces at this time, but no repetition of the treatment was attempted.

In June of the next year the patient was seen again. He was well nourished, lively, and intelligent, but, although in good condition, was not entirely cured of his former trouble. The strabismus was still present, and the lateral movement of the head still occurred, but only at intervals. For some days he had been suffering again from diarrhea. Two months before also he had had an attack of abdominal pain with fever, which lasted two days. The feces contained eggs of *Hymenolepis* and *Trichuris*. After treatment with male fern and calomel, about 100 *Hymenolepis* were passed.

At an examination made about one year later, the feces were found entirely free from *Hymenolepis* eggs, but containing an abundance of *Ascaris* eggs. The clonic spasms of the neck still continued, due perhaps to the reflex irritation from the *Ascaris*.

*Case No. 50.*—Rossini, of Pisa, treated a well-to-do young man, 20 years old, from Pescia, near Pisa, for *Tenia*. Besides a *Tenia saginata*, about 1,000 *Hymenolepis nana* were passed as a result of the treatment, and the specimens were referred by Rossini to SOSSINO (1895a) for determination. An anamnesis of this case could not be procured.

**St. Petersburg, Russia, 1890** ..... 1 case.

*Case No. 51.*—In 1890 PROFESSOR AFANASYEFF, according to GUSEFF (1892a, 1893a), found a case of *Hymenolepis nana* at St. Petersburg.

**Moscow, Russia, 1892** ..... 1 case.

*Case No. 52.*—GUSEFF (1892a, 1893a) reports a case of *Hymenolepis nana* in a child 1½ years old at Moscow. About 200 worms were passed after treatment. This case is also mentioned by ZOGRAF (1893).

**Cologne, Germany, 1892** ..... 1 case.

*Case No. 53.*—The first case of infection with *Hymenolepis nana* in Germany was reported from the Bürger-Hospital, at Cologne, by LEICHTENSTERN (1892), and more at length by MERTENS (1892).

A boy 6 years old was brought to the hospital in March, 1892, to be treated for *Oxyuris*. According to his mother he picked at his nose a great deal, had never shown, however, any symptoms of intestinal disorder, nor had he ever suffered from any nervous affection. Examination showed the patient healthy in every respect. Feces were normal in color and consistency, with an occasional *Oxyuris*, and eggs of *Hymenolepis nana*. Santonin was administered for 3 days in doses of 0.025 grams daily. *Oxyuris* were passed, but no tapeworms. Five grams of male fern in 2 doses, followed by salts, were then tried, and 300 to 350 *Hymenolepis* were passed. The patient experienced no bad effects from the treatment and left the hospital in a day or two. Eggs were not present in the feces until after a lapse of about 15 days, when they reappeared. In May the boy returned to the hospital. A number of enumerations gave a result of 6,400 eggs to 1 cc. of feces. Three doses of male fern, 2.5 grams each, followed by salts, were administered, and 305 worms



were passed. An hour or two after the last dose the child became very restless, and cried on account of pain in the abdomen. The abdomen was hard and tense, but not swollen; the legs were doubled up. Severe and repeated vomiting occurred. The first and second vomiti had the characteristic odor of male fern. The abdominal pains ceased in the afternoon, but the vomiting continued until late in the night. On the 13th day eggs again appeared in the feces. On the 20th day there were 1,500 eggs in 1 cc. of feces. In June thymol was tried, but no worms were passed, and the eggs continued present in the same number. Three days later 8 grams of male fern in 3 doses, which were well borne, were administered, and 70 worms were passed. On the 14th day eggs again appeared.

Numerous *Oxyuris* were expelled at each treatment. Charcot-Robin crystals were not present in the feces.

**Naples, Italy, 1892-1896** ..... 4 cases.

Out of 73 children, aged from 1 month to 12 years, examined in the pediatric hospital at Naples, CIMA (1893a, 1896a, 1896b) reports 34 cases of helminthiasis, 4 of which were infections with *Hymenolepis nana*.

*Case No. 55* (Cima's Case 33).—Boy, aged 8 years, from the city, showed a slight trace of rachitis. Feces contained eggs of *H. nana*. During a single day's stay at the hospital he gave no signs of disturbances which could be traced to the action of parasites.

*Case No. 55* (Cima's Case 56).—Boy, 7 years, from the city, chronic intestinal catarrh. He was brought to the hospital on two occasions. According to his father, the boy had suffered for two years with a bloody diarrhea, and had grown thin and pale. "Feces showed elements common to those of anemic patients," and eggs of *Hymenolepis nana* were observed in every preparation. Rectal injections of boric and tannic acids were prescribed, with what effect is not known as the patient was not seen again.

*Case No. 57* (Cima's Case 65).—Girl, 10 years, from the city, with nervous disturbances. Fifteen days before entering the hospital the patient began to experience difficulty in walking, and in four or five days the trouble became so pronounced that she was not able to leave her bed; at night she complained of pains in the shoulders, loins, and legs. The pains diminished after a few days but an uncertainty in the gait remained, together with a sensation of formication and itching of the trunk, especially in the mammary region. No disturbances in the movements of the hands or arms were observed. The gait resembled that of ataxic or choreic subjects. The left leg dragged a little also. When the eyes were closed, the gait became more incoordinated, she often tottered, and would fall if not supported. There were no pains in the spine or legs, the general sensibility and special senses were intact; patellar reflexes were a little exaggerated; electrical tests showed nothing abnormal. The symptoms could not be assigned to any known clinical type, and rest and a hygienic diet were prescribed. In a day or two the symptoms ameliorated, the left leg was no longer dragged; blindfolded, she still walked badly, with a tendency to turn to the right. On the fourth day she was able to walk more freely with the eyes covered, and in a few days more the gait became entirely normal. During her stay at the hospital the girl passed about 75 grams of feces, 3 to 4 times per day. Since every microscopic preparation of less than 1 mg. of feces contained 2 or 3 eggs of *Hymenolepis nana*, an enormous number of parasites must necessarily have been present. Some *Trichuris* eggs were also present. No special anthelmintic treatment was attempted. Cima thought it very likely that the nervous disturbances were to be attributed to the excitation of the intestinal sympathetic plexus from the irritation set up by the heads of the parasites embedded in the mucosa.

*Case No. 57* (Cima's Case 67).—Boy, 3 years, from the city, abdominal tuberculosis. This case was a typical one of abdominal tuberculosis, from which death



finally occurred. Eggs of *Ascaris*, *Trichuris*, and *Hymenolepis nana* were present in the feces.

In none of the above four cases were Charcot-Robin crystals found in the feces.

**Catania, Sicily, 1895** ..... 23 cases.

*Cases Nos. 58 to 80.*—VENUTI (1895) (referred to by MASSARI, 1898, p. 213) observed in the Reale Ospizio di beneficenza di Catania, 23 cases of *Hymenolepis nana* in 214 boys examined. Most of these cases harbored a considerable number of worms, while in 100 boys of the general population belonging to diverse classes and in widely differing conditions of life he could not find a single case. The lack of cleanliness among the inmates, the intimate association of some of those affected with worms, the appearance of subjective disturbances in others after they had been in the institution a certain length of time, ceasing rapidly after the expulsion of the parasites, were circumstances which Venuti considered indicative of the occurrence of a direct contagion of endemic character.

**Cologne ?, Germany, between 1892 and 1896** ..... 1 case.

*Case No. 81.*—HUBER (1896a, p. 573), upon the basis of a personal letter from Leichtenstern, records a case of *Hymenolepis nana* in Germany. A boy 7 years old, suffered 1½ years from nocturnal enuresis, which disappeared after the evacuation of the parasites.

**Cologne, Germany, 1894** ..... 1 case.

*Case No. 82.*—In a table of cases of helminthiasis, BÜCKLERS (1894a) records the case of a girl, 7 years old, in whose feces a few eggs of *Hymenolepis nana* were present. Charcot-Robin crystals were absent. Blood examinations showed eosinophile cells, 7 per cent; polynuclear, 42 per cent; mononuclear, 42 per cent; transition forms, 9 per cent.

**Rome, Italy, 1896** ..... 1 case.

*Case No. 83.*—MASSARI (1896, 1898, p. 212) in 1896 determined the presence of *Hymenolepis nana* in Rome by finding the eggs in the feces of a little girl 7 years of age.

[? **Catania, Sicily**], **Italy** ..... 2 cases.

*Case No. 84.*—GALVAGNO (? date) found numerous *Hymenolepis nana* in one of his little girls (referred to by MASSARI, 1898, p. 213).

*Case No. 85.*—Feletti (MASSARI, 1898, p. 213) found one of his little girls infected with *Hymenolepis nana*.

**Cologne and Bonn, Germany, 1897-98** ..... 1 case.

*Case No. 86.*—The case of a little girl 2¼ years old is reported by RÖDER (1899) from the medical clinic at Bonn.

The child is well nourished, the mucous membranes are perhaps somewhat paler than usual. The bowels are regular, and there is no apparent organic trouble. Until 4 months before, she had lived in Cologne. At 13 months she suffered from intestinal catarrh and cankered mouth, at 18 months passed an *Ascaris*, and at 2 years had measles. After this she became pale, her appetite diminished, she grew dull and drowsy, blue rings appeared under the eyes, and she picked at the nose. Anthelmintics were administered, but no worms were seen.

The patient was brought to the hospital and placed under anthelmintic treatment, August 19, 1897. Three 0.05 gram doses of calomel were given and the next morning, after 80 grams of milk, 2.5 grams of ethereal extract of male fern, followed by a purge of castor oil, were given. In the stool which resulted, numerous eggs of *Ascaris* and eggs of *Hymenolepis nana* (3 to 4 in each preparation), but no worms were found. For several days following, eggs of *Ascaris*, but none of *Hymenolepis*,

were present in the feces. On September 1, *Hymenolepis* eggs were again numerous. The next day three 0.05 gram doses of santonin were given an hour apart, followed by castor oil, but neither *Hymenolepis* nor *Ascaris* was found in the passages. *Hymenolepis* eggs were not found again up to the time the child was removed from the hospital on the 9th of September. In December an examination of feces from the child showed numerous *Ascaris* eggs, and an average of one *Hymenolepis* egg in each preparation.

The child was returned to the hospital March 15, 1898. At that time she was in poor physical condition. She was suffering from conjunctivitis, scrofular keratitis, rhinitis, eczema of the scalp, with glandular swellings in the neck, axilla, and groin. Pulse was 120. The feces as before contained eggs of *Ascaris* and *Hymenolepis*. During the afternoon of the 18th two teaspoonfuls of castor oil were administered, which had no effect. The next morning a tapeworm remedy (Bandwurmtritöl Helfenberg), in a dose equivalent to 5 grams extract of male fern, was given, followed in half an hour by two teaspoonfuls of castor oil. Some of the remedy was thrown up, but 4 grams more of the extract (in the same preparation) was given with the oil. Three-quarters of an hour later an enema of 10 grams of glycerin was also given. In the stools which followed no worms, but only eggs of *Ascaris* and *Hymenolepis*, were to be found.

Nine months later, in December, the stools were examined and found entirely free from eggs.

Bearing in mind the possibility of infection from infested rats or mice, Röder examined two of the houses at Cologne in which the patient had lived, and found them free from rats. Several examples of mice which were caught there contained no worms. The new abattoir of Cologne was also free from rats.

### Moscow, Russia, 1900 ----- 1 case.

*Case No. 87.*—A curious case, possibly of *Hymenolepis nana*, has been reported by PREDTETS-CHEMSKY (1900) from the propedeutic clinic of Moscow University.

The patient was a female, 33 years old, wife of an officer, and had never been in the Tropics. She was suffering from chyluria of some 16 years standing. In one of the numerous microscopic preparations which were made of the urine sediment there were found about 10 specimens of what appeared to be cestode eggs, resembling in size and structure those of *Hymenolepis nana*. These bodies were round with a laminated capsule and were so transparent that the six hooks, characteristic of cestode embryos, were clearly distinguishable under an immersion lens. In size the eggs measured 20 to 25  $\mu$ . In no other preparation were the eggs seen. Accidental contamination seemed, *a priori*, very evident, and since the vessel in which the urine had been collected had been carefully cleaned with boiled water, suspicion was directed toward the feces of the patient, which were examined several times, but always without the discovery of any tapeworm eggs. The riddle therefore remained unsolved. The remarkable coincidence of the eggs of the rare parasite *H. nana*, and the rare disease, non-tropical chyluria, was commented upon by the author. He further cites the instance of a case of chyluria in Madagascar, observed by Doctor Ollivier, in the analysis of which M. Bordier is said to have demonstrated the presence of *Davainea madagascariensis* in the kidneys, and considers it possible that *Hymenolepis nana* may also settle in the urinary organs and give rise to a true chyluria.

There are a number of possibilities in connection with this case: First, that the eggs were passed in the urine; second, that they came from the feces of the patient; third, that they were from the feces of another person, or that they were eggs resembling the eggs of *Hymenolepis nana* from a tapeworm of some animal, bird, rat., etc., and came by some fortuitous circumstance into the preparation.

There are two objections to the first possibility, namely, the unusual occurrence of

cestode eggs in the urine, and the fact that they were found in but one preparation, so that this possibility remains very improbable, notwithstanding the attendant chyluria. The second possibility is quite probable, since the eggs of *Hymenolepis nana* not only are often difficult to find, but frequently disappear spontaneously from the feces and later recur again, so that even a large number of examinations might fail to disclose the presence of the parasite. Even the most extreme care in technique is insufficient to entirely exclude the last-named possibility.

The authenticity of this case is therefore extremely doubtful.

#### ASIA.

Siam, 1892..... 1 case.

*Case No. 88.*—In September, 1892, RASCH (1894) was consulted by a native girl, 7 years of age. The patient had suffered for a long time with sleeplessness. There was no organic trouble. She was constipated, so that cathartics were frequently necessary. Vomiting was of common occurrence, especially in the morning, which was not due to overeating, as she had but little appetite. The stools were usually mixed with copious quantities of mucus. Temperature, pulse, heart, lungs, abdomen were normal. The patient appeared somewhat pale and anemic, and blue rings were often present under the eyes. Her general physical condition was fairly good. An examination of her feces showed the eggs of *Hymenolepis nana*, larval nematodes [*Strongyloides stercoralis*] and a female *Oxyuris vermicularis*. After treatment with male fern, 50 to 80 specimens of *Hymenolepis nana* were isolated from the stool.

Tokyo, Japan, 1895..... 2 cases.

*Cases Nos. 89 and 90.*—MURA & YAMAZAKI (1897) report two cases from Japan.

The first case was that of a boy of 5 years, who had been received in 1893 at the poorhouse with his mother. In June, 1895, he became ill of a fever, with enlargement of the liver and spleen. The feces contained eggs of *Oxyuris*, *Trichuris*, and *Hymenolepis*, but the patient showed no reflex nervous symptoms which might be traced to helminthiasis. When the fever had improved somewhat the boy was dosed with a decoction of pomegranate, followed by castor oil. Many *Oxyuris* were passed, but no *Hymenolepis*. Two days later, besides the pomegranate decoction and oil, male fern was also administered. A large number of *Hymenolepis* were passed, of which over 150 were isolated. After three weeks the eggs again appeared in the feces, and 15 more tapeworms were passed after doses of male fern and salts.

*Case No. 90.*—The second case, also observed in 1895, was a foundling, girl, aged 5 years, who had entered the poorhouse the year before. After a while she became thin and anemic, suffered from irregular attacks of remittent fever and diarrhea. Examination of the thoracic and abdominal organs gave mostly negative results; the abdomen was rather sensitive to pressure. The eggs of *Trichuris*, *Oxyuris*, *Ascaris*, *Agchylostoma*, and *Hymenolepis* were found in the feces. Hookworm eggs were seen only after 60 preparations were examined, and those of *Hymenolepis* only after 70 preparations. After treatment with pomegranate and male fern, two specimens of *Hymenolepis nana* were passed.

#### AMERICA.<sup>a</sup>

Philadelphia, Pa., 1872..... 1 case.

*Case No. 91.*—SPOONER (1873a, b), on September 3, 1872, presented to the College of Physicians of Philadelphia some specimens of *Hymenolepis nana* from the first case observed in America. They were passed by a young man who had symptoms of general debility, occasional colicky attacks, diarrhea, severe frontal headache, disturbance of vision, with slight febrile exacerbations, occurring at irregular inter-

<sup>a</sup>See also footnote, p. 7.



vals during the two weeks preceding the above date. Up to the time of the report no marked emaciation had occurred; the appetite was less fitful, and the vision more perfect, but the pain in the head had not much abated.

**Buenos Ayres, Argentina, 1886** ..... ? 1 case.

*Case No. 92.*—According to O. WERNICKE (1890, p. 351), Dr. Roberto Wernicke, in 1886, observed in the feces of a little girl cestode eggs, which he was unable to identify as belonging to any species known to him. He administered a vermifuge, but did not succeed in finding any worms. After seeing the eggs from O. Wernicke's case (1890), Dr. R. Wernicke expressed the opinion that the eggs found by him in 1886 were of the same species.

**Buenos Ayres, Argentina, 1890** ..... 1 case.

*Case No. 93.*—WERNICKE (1890) found 30 to 40 specimens of *Hymenolepis nana* in the intestine, at the autopsy of an Argentine sailor, aged 28 years, who had died of pulmonary tuberculosis. This case was also reported and the specific determination confirmed by BLANCHARD (1891a).

**São Paulo, Brazil, 1893-1894** ..... 2 cases.

LUTZ (1894) reports two cases of *Hymenolepis nana*, also a case of *Hymenolepis diminuta*. (See p. 98.)

*Case No. 94.*—The first case was that of a 2½-year-old girl who had shown symptoms of nervous and intestinal troubles for about a year. Several times she suffered from irregular attacks of fever, and showed other symptoms common to the teething period. Ascarids were passed on several occasions. During one of the attacks of fever the feces were examined; encysted flagellates and eggs of *Trichuris* and of *Hymenolepis nana* were found. After the fever had subsided, a treatment with ethereal extract of male fern resulted negatively. A second attempt was made with freshly obtained extract in three doses of 0.3 gram each at intervals of two hours, and in the stool after the first dose 5 strobilæ, without recognizable heads, were obtained. There was a slight improvement for a while, but the former symptoms of abdominal pain, diarrhea, restless sleep, and pained expression of countenance, soon returned. Male fern was again administered in a 3-gram dose, and about 100 *Hymenolepis*, 15 of them with heads, and 2 female *Trichuris* were expelled. Two weeks later the child was much improved, but not entirely well.

*Case No. 95.*—The second case was a 4-year-old girl, born in São Paulo, of foreign parents. She had suffered for two years with continual diarrhea and intermittent attacks of fever. Carefully regulated diet and treatment in Europe, had had no ameliorating effect. There were symptoms of perverted appetite, eating of plaster from the wall, etc., while the nervous symptoms were little pronounced. Contrary to what one would expect from the length of time the trouble had lasted, the nutrition had not suffered to an appreciable extent, a circumstance due perhaps to the care which the girl had received. After the discovery of eggs of *Hymenolepis nana* in the feces 4 grams of ethereal extract of male fern in emulsion were administered, and two passages containing an enormous number of worms occurred. In an incomplete enumeration, over 2,000 individuals were counted, of which about 10 per cent had heads. Little chains of ripe segments were also common. About three weeks later, the extract was again given, in a dose of 2.5 grams, and 25 worms were passed. All symptoms of the former trouble disappeared, and while previously the diarrhea had persisted in spite of all carefulness in diet, the stools became normal and so remained, although the girl now ate anything she pleased.

**Galveston, Tex., 1902** ..... 1 case.

*Case No. 96.*—MOORE (1903)<sup>a</sup> has reported a case of *H. nana* from Texas, in a preliminary note read recently before the University of Texas Medical Club.

<sup>a</sup>See also Moore (1904).



"On August 2, 1902, T. O. C., a section foreman of the Galveston, Houston and Henderson Railway, presented himself, complaining of a severe diarrhea and cramps in the abdomen. His history was as follows:

"Family history good. No previous sickness of any kind. Present illness began in the early part of June, 1902, with headaches and a slight fever. About July 28, he was taken with a severe diarrhea and much pain in the bowels. He had from ten to twenty stools per day. Passed mucus and blood in the motions. Suffered great weakness.

"He was given a diarrhea mixture and asked to return in case he was not relieved. He came back on August 4, stating that he was no better."

Amebic dysentery or the presence of some intestinal worm having been suspected, an examination of the feces was made which resulted in the discovery of the eggs of *H. nana*, and after the administration of an anthelmintic, a number of the worms themselves were passed. The effect upon the symptoms of the expulsion of the worms is not stated in Doctor Moore's paper. The specific determination of the parasites in this case was confirmed in this laboratory.

**Charleston, S. C., 1902** ..... 1 case.

*Case No. 97.*—STILES (1903a, p. 40), in October, 1902, while examining some of the students of the Charleston, S. C., Medical School, found that the stools of one of them (Mr. T.) contained numerous eggs of *Hymenolepis nana*. The young man was 22 years of age, and came from the country. Later examinations showed that he was also infected with *Uncinaria americana*. The symptoms in this case, from what information I have, seem to have been only very slight. The patient complained of a certain degree of nervousness. Dr. J. L. Dawson, who has expressed the intention of publishing a full clinical history of this case, after the discovery of the eggs, placed the patient upon anthelmintic treatment. In a letter to Doctor Stiles he states that hundreds of the worms were passed. Doctor Dawson kindly furnished this laboratory with specimens from this case, which have been entered in the Helminthological Collection (No. 9402) of the United States Public Health and Marine-Hospital Service.

**Macon, Ga., 1902** ..... 3 cases.

In November, 1902, while examining 39 children in two orphan asylums at Macon, Ga., STILES (1903a, p. 41, 42) found 3 cases of infection with *H. nana*. The patients were as follows:

*Case No. 98.*—R. J., female, 11 years old, from Lumber City, Telfair County, Ga.; a case of light infection.

*Case No. 99.*—M. N., female, 13 years old, from Taylor County, Ga.; a case of very heavy infection.

*Case No. 100.*—O. H., male, 16 years old, from Wright, Wilcox County, Ga.; a case of light infection.

We have no data as to the symptomatology of these cases, nor any information with regard to the results of treatment, if such were tried.

**Washington,<sup>a</sup> D. C., 1903** ..... 6 cases.

In a series of about 2,000 fecal examinations of patients at the Government Hospital for Insane at Washington, made during 1902–1903 in this laboratory, the eggs of *Hymenolepis nana* were encountered six times.

*Case No. 101.*—The patient in this case was a woman (white); aged, about 60; an inmate of the hospital for a good many years. Shortly after the examination, when the eggs were discovered, the patient was sick for several days. We have had no information as to the exact nature of the ailment. Specimens of several stools taken during this time were liquid in character and no eggs were to be found, nor were any

<sup>a</sup> See also footnote, p. 7.

eggs seen in preparations of the stools of this patient examined on one or two occasions after her recovery.

*Case No. 102* (Gov. Hosp. case No. 9901).—I. L., colored; age, 32; born in Virginia; admitted to the hospital in May, 1896, suffering with chronic dementia which had lasted one year; supposed cause, masturbation. He has been an inmate of W. L. building continuously since 1900, and of ward 3 of this building since April 11, 1903. He is said to be in good physical condition and works in the power house. In July, 1900, he was sick for a few days and lost considerable flesh; but, after treatment for three days with an ague mixture, improved and was soon back at work. In October, 1901, he was affected with a skin disease resembling itch, which disappeared after local treatment with iodine. Eggs of whipworm (*Trichuris trichiura*) and of *Hymenolepis nana* were present in his feces in May, 1903.

*Case No. 103* (Gov. Hosp. case No. 9376).—E. Q., colored; indigent; age, 32; born in District of Columbia; admitted to hospital November, 1894, with congenital imbecility. He has been an inmate of W. L. building continuously since August, 1899, and of ward 3 since February, 1902. His weight has ranged from 222 to 232. He has been detected at various times masturbating, and during these periods he has been more demented. Physically he remains in good health. Eggs of *H. nana* were seen in the feces in 5 out of 10 preparations examined; whipworm eggs were also present.

*Case No. 104* (Gov. Hosp. case No. 12804).—H. J., colored; sergeant (retired). U. S. Army; cook; age, 51; admitted to hospital from Army General Hospital, Presidio, Cal., November, 1901, with delusional melancholia of six months' duration, supposed cause organic brain disease. He has been an inmate of ward 3 of W. L. building, continuously since March, 1902. At a physical examination in November, 1901, he was found to be fairly well developed; his abdomen was tense, rounded, and tympanitic; his bowels were constipated. Muscular movements were slow and weak; coordination was fair. Muscle reflexes were diminished, tendon reflexes normal. He suffered at times with vertigo. Opacity of both crystalline lenses was present. His mental symptoms were false perception, poor memory, false ideation, poor reasoning and judgment, delusions and auditory hallucinations. In habits he is fairly cleanly. An examination of his urine, November 11, 1901, showed a slight hematuria, which had entirely disappeared ten days later. He suffered from malaria (tertian type) for a few days in November, 1901, but recovered promptly after treatment. In May, 1903, the eggs of *H. nana* were found in the feces in 7 out of 10 preparations examined.

*Case No. 105* (Gov. Hosp. case No. 10953).—C. G., colored; indigent; age 47; born in Maryland; admitted to hospital October, 1898, with chronic mania of 20 years' duration; supposed cause prison life. He has been an inmate of ward 3, W. L. building continuously since February 1901. His health is reported good and appetite excellent. This case was a heavy infection; numerous eggs were found in the feces, in all of 10 preparations examined, May, 1903; whipworm eggs were also present.

*Case No. 106* (Gov. Hosp. case No. 8857).—J. S., colored; indigent; age 40; born in Florida; admitted to hospital July, 1893, with acute melancholia of three months' duration; supposed cause, masturbation. He has been an inmate of ward 3, W. L. building, continuously since February, 1901. In the fall of 1901 he suffered for some time with a skin disease resembling itch, localized in the neighborhood of the genital organs. The eruption became better, and finally disappeared after local treatment with iodine. He is said to be in good health, with good appetite, sleeps well, works in the vineyard. In May, 1903, fecal examination showed eggs of *H. nana* in 7 out of 10 preparations. Eggs of *Trichuris* were also present.

It is a noteworthy circumstance that of the six cases of *H. nana* at the insane hospital, five were found among colored patients, all inmates of the same building and

the same ward. This fact fits in very well with the assumption that a direct infection occurs from one person to another, and is evidence similar to that brought forward by Venuti (see p. 55).

## ANALYSIS OF CASES AND DISCUSSION OF SYMPTOMS.

### AGE AND SEX OF INDIVIDUALS AFFECTED.

In the 106 cases of *H. nana*, at least 60, and probably 70, of the individuals affected were males: 30 were females, while in the reports of the remaining 6 cases the sex is not indicated. Sixteen and probably 18 were over 20 years of age, 2 at least being over 50; 84 were younger than 20 years; in 4 cases no reference is made to age. Between 1 and 5 years there were 9 cases; 5 and 10 years, 24 cases; 10 and 15 years, 5 cases; 15 and 20 years, 5 cases; 41 other cases were reported simply as children.

According to these figures *Hymenolepis nana* is much more common among children than among adults, and males are more often infected than females. Five to 10 years seems to be the age most frequently affected. The very large percentages of males and children may be due in some degree to the fact that in the more heavily infected regions investigations have been made more especially among children than among adults, and among males than among females.

### GENERAL ENVIRONMENT AND SOCIAL POSITION OF INFECTED INDIVIDUALS.

With regard to the social position and general environment of the individuals affected, it is to be noticed, in the first place, that 32 of the cases were in orphan asylums or poorhouses, 27 being in the asylum at Catania, Sicily; 3 in two asylums at Macon, Ga., and 2 in a poorhouse at Tokyo, Japan; and 6 cases were in an insane asylum in the District of Columbia. Of the remaining cases, 6 or 8 may be said to belong among the well-to-do classes. Grassi, also (Grassi & Rovelli, 1892a), as already stated, refers to an indefinite number of cases which occurred among the children of well-to-do families. It is only certain that the patients in about 20 of the 62 cases remaining were poor, but it is probable, judging from various circumstances related in connection with individual cases, that the majority were from the poorer classes.

The conclusion does not, therefore, seem unjustified that the children of the poor are more liable to infection, and children gathered together in institutions seem especially likely to show a heavy percentage of infection; the worm, in fact, seems to be particularly common in orphan asylums. Among adults, also, institutional life seems to favor infection (cases Nos. 101 to 106).

There are about 47 cases which can be assigned to the city as against 15 to the country (including the cases from the asylums [except the Macon cases] among the former). Investigations have been made, however, mostly among city inhabitants.

#### PREVALENCE OF INFECTION.

At many of the hospitals in Germany a large number of examinations for parasites are made every year, but so far only 4 cases of *Hymenolepis nana* have been reported from that country. Mertens (1892, p. 1136) states that 300 to 400 patients, mostly adult however, are examined yearly at the Cologne Hospital, and that formerly the eggs of *Hymenolepis nana* had never been found. After the discovery of the eggs of the parasite in the feces of a child who had entered the hospital, 100 other children, at that time in the hospital, were carefully examined for evidences of parasitic infection. Although 14 cases of helminthiasis were found, *H. nana* was not present.

In Italy the parasite is decidedly common. Calandruccio estimates that in Sicily 10 per cent of the children are affected.

Venuti (1895), according to Massari (1898), determined the ratio of infection among 214 boys in the orphan asylum at Catania to be over 10 per cent (23 cases), while among 100 boys from various classes of the general population he was unable to find a single case.

Out of about 2,000 fecal examinations made at this laboratory during 1902-1903, of adult patients at the Government Hospital for the Insane, Washington, D. C., the eggs of this parasite were encountered 6 times.

Stiles (1903a, pp. 41, 42), in about 160 fecal examinations made during a recent trip through the South Atlantic States in connection with an investigation of uncinariasis, found the eggs of *Hymenolepis nana* 4 times, once in the examinations of 15 medical students, and 3 times among 39 children in 2 orphan asylums.

#### GEOGRAPHIC DISTRIBUTION OF *Hymenolepis nana*.

Geographically the cases of *Hymenolepis nana* in man are distributed as follows:

Egypt, 3 cases; England, 1 case; Sicily, 48 cases; Italy, exclusive of Sicily, 27 cases; Russia, 2 cases and 1 doubtful case; Germany, 4 cases; Servia, 1 case; Siam, 1 case; Japan, 2 cases; Pennsylvania, 1 case; District of Columbia, 6 cases; South Carolina, 1 case; Georgia, 3 cases; Texas, 1 case; Brazil, 2 cases; Argentine, 1 case and 1 doubtful.

The worm has been reported from rats or mice in the following places:

Austria (Stossich, 1898, p. 104); Denmark (Krabbe, 1865, p. 39); Germany (Grassi, 1887h, p. 312; Linstow, 1896a, p. 579; Moniez, 1888); France (Dujardin, 1845a, Moniez, 1888); Italy, including Sicily (Grassi,



Calandruccio); United States (specimens in the B. A. I. Coll., U. S. Dept. of Agr., collected in Maryland and the District of Columbia); Brazil (Lutz, 1894).

The figures seem to show that a rather warm and moist climate is especially favorable to the development of cases of *Hymenolepis nana*. As would be expected upon the assumption that the forms in man and in the rat are the same species, the statistics indicate a certain degree of coincidence in the occurrence and frequency of *H. nana* in man and in the rat for any locality, modified, it is true, by other factors, such as the hygienic conditions of the community, the habits and customs (personal hygiene, character of food) of the inhabitants, etc. In general its distribution may be considered cosmopolitan, like that of its hosts, but more restricted by certain conditions, among which are, perhaps, climate and moisture.

#### SITUATION IN THE INTESTINE.

The results of a number of autopsies show that the portion of the intestine infested is a greater or less part of the ileum, especially its upper two-thirds or three-fourths.

#### NUMBER OF SPECIMENS PRESENT.

The number of specimens of *H. nana* present in the various cases has ranged from 1 to several thousand. In one case, 1 specimen only was found at the autopsy; 2 specimens were passed in one case; 20 were present in one case; 30 to 40, 1 case; 50, 1 case; 50 to 80, 1 case; between 100 and 200, 2 cases; from 200 to 400, 4 cases; 600 to 700, 1 case; 1,000, 1 case; 1,400, 1 case; 2,000, 1 case; in 5 cases in which no figures were given there were said to be few; in 7 cases a very large number or several thousand.

#### OTHER PARASITES PRESENT.

Multiple infection occurred in 27 cases. *Oxyuris vermicularis* was present 12 times, *Trichuris trichiura* 19 times, *Ascaris lumbricoides* 16 times, *Agchylostoma duodenale* 5 times, *Uncinaria americana* once, *Tænia saginata* 2 times, *Tænia solium* once, encysted flagellates once, larval nematodes [? *Strongyloides stercoralis*] once. They were associated together with *H. nana* as follows:

*Trichuris*, 6 cases; *Ascaris*, 3 cases; *Oxyuris*, 2 cases; *Agchylostoma duodenale*, 1 case; *Uncinaria americana*, 1 case; *Tænia saginata*, 2 cases; *Oxyuris* and *Trichuris*, 1 case; *Oxyuris* and *Tænia solium*, 1 case; *Oxyuris* and larval nematodes [? *Strongyloides*], 1 case; *Oxyuris*, *Trichuris*, and *Ascaris*, 6 cases; *Trichuris* and *Ascaris*, 2 cases; *Trichuris*, *Ascaris*, and encysted flagellates, 1 case; *Trichuris*, *Ascaris*, and *Agchylostoma duodenale*, 2 cases; *Ascaris* and *Agchylostoma duodenale*, 1 case; *Oxyuris*, *Trichuris*, *Ascaris*, and *Agchylostoma duodenale*, 1 case.

## DURATION OF INFECTION.

The duration of infection as determined by the actual observation of eggs in the feces after the time they were first seen was 2 months in one case (No. 43), 6 months in 3 cases (Nos. 36, 45, 53), 7 months in 2 cases (Nos. 48, 86), 1 year to 2 years, 3 cases (Nos. 4, 47, 49), 2½ years, 1 case (No. 38).

As determined also by the length of time the symptoms existed, which were cured or improved by anthelmintic treatment: 3 months, 1 case (No. 42); 7 months, 1 case (No. 41); 1 to 2 years, 7 cases (Nos. 37, 43, 44, 49, 81, 94, 95); 5½ years, 1 case (No. 38). In 1 case (No. 36) the symptoms disappeared spontaneously after lasting 6 months, reappeared after a lapse of 1½ years, then disappeared again after anthelmintic treatment, but recurred with the reappearance of eggs in the feces.

In cases which were not treated the symptoms lasted 3 years, ending in death in 1 case (No. 9); and for 2 years in another case (No. 55); in a third case (No. 48) symptoms, which may have been caused by the presence of *H. nana*, were exhibited for nearly 6 years.

## GENERAL SYMPTOMATOLOGY OF INTESTINAL HELMINTHIASIS.

Before taking up the analysis of symptoms exhibited in cases of *Hymenolepis nana*, it is considered advisable to review shortly the symptomatology of other intestinal worms, especially tapeworms. Generally speaking, the injurious effects of intestinal worms may be looked upon as due to one or more of the following causes, namely, the mechanical obstruction occasioned by their presence, the irritation to the wall of the intestine, the influence of this irritation upon the nervous system, the loss to the host of nutritive materials which go to supply the parasites, and finally, the elimination by the parasites, of toxic principles which are absorbed by the host.

In discussing the phenomena produced by worms, Davaine (1860a, pp. 48 et seq.), the eminent French helminthologist, says in part essentially as follows:

The presence of worms in the intestine does not always result in appreciable phenomena: it is compatible with the most perfect health; but is frequently manifest by variable phenomena of a local and often of a sympathetic nature.

The local phenomena consist of derangements of the intestinal functions, abdominal pains, anal pruritus, and occasionally anatomical lesions of some importance.

Any organ may be affected reflexly by intestinal worms; false perception of odors, dilation of the pupil, permanent or transitory amaurosis, abnormal sensitiveness of hearing, perversion of taste, itching and formication of the skin, bear witness to the sympathetic action of the parasites upon the senses: from another side, somnolence, vertigo, frightful dreams, spasms, vague pains, cough, dyspnea, cardiac palpitations, irregularities of pulse, insatiable hunger or anorexia, salivation, quality of the urine,

emaciation, witness equally their action upon the nervous system, upon the organs of respiration, upon the circulation, upon the digestion, upon the secretions, and upon the nutrition. While the sympathetic effect of intestinal worms upon organs more or less remote, and the functional disorders which they occasion can not be denied, one ought not, on the other hand, to display the ignorance and prejudices characteristic of a former epoch, by accepting without scrutiny all the accounts which have been transmitted to us, even when coming from most eminent men. Although very grave symptoms are sometimes unquestionably determined by intestinal parasites, doubt and caution should compel us to suspend judgment in very many cases where the presence of worms and illness may only be a simple coincidence.

The absence or appearance of functional troubles, their frequency or variable intensity is not explained by differences in the nature of intestinal worms. *Tenia*, *Bothriocephalus*, *Ascaris*, or *Oxyuris* may all give rise to similar phenomena. The number or the size of these entozoa is undoubtedly not without influence upon the development of pathologic phenomena; their presence seems to be less easily supported in the stomach than in the intestine; but in certain cases, neither the species nor their number or size, nor the part of the intestine which they occupy, accounts for the variations or the intensity of the symptoms, which often depend upon bodily peculiarities and the degree of susceptibility of the individual affected; in fact, women experience ordinarily the most severe derangement of health, and feeble and nervous individuals are also more affected than those in better condition. (Translation.)

Davaine says further (1860a, pp. 103 et seq., in part):

The principal symptoms of *Tenia* are giddiness, humming in the ears, disorders of vision, nasal and anal pruritus, salivation, disorders of appetite and digestion, colic, pains in the epigastrium and other regions of the abdomen, cardiac palpitation, syncope, sensations of a ball or weight in the abdomen rolling about and following the movements of the body, pains and lassitude in the limbs, and emaciation.

The abdominal pains caused by *Tenia* may be of the nature of colic or of gastralgia; frequently their character is difficult to appreciate. They are referred to different parts of the abdomen, are of varying severity, sometimes lively and intermittent, and are ordinarily not accompanied nor followed by diarrhea. They constitute the most common symptom of *Tenia*.

Anal pruritus is also a very common phenomenon. While, in some cases, it may, like nasal pruritus, be attributed to a sympathetic influence, it is usually due to irritation of the lining of the lower part of the intestine, produced by the contact and movements of detached segments. Itching of the nose is less frequent, but it is rare that an individual affected with *Tenia* does not suffer from either nasal or anal pruritus.

The appetite is often augmented, sometimes insatiable; at other times it is lacking or subject to alternate augmentation and diminution.

There exist very often among persons affected with *Tenia* a general debility, lassitude, cramps, and pains in the extremities, sufficiently severe to interfere with the usual occupation.

Emaciation is very common when the infection is of long standing. Sometimes it is accompanied with bloating and distension of the abdomen.

The greater part of these phenomena do not have very serious effects upon the individuals affected; but it is different with certain convulsive symptoms which develop under the influence of *Tenia*. These consist in attacks of more or less similar nature, presenting the characteristics of epilepsy, hysteria, chorea, etc., in some cases very intense and severe. These functional disorders are the most frequent among those brought about by the presence of *Tenia* and disappear with the expulsion of the parasite. This coincidence and the fact that the symptoms do not recur leaves no doubt as to their cause. (Translation.)



Numerous cases are referred to by Davaine in which epileptiform attacks, chorea, tremors, paralysis, cough, bulimia, perversions of sense, weakening of the mental faculties, or deafness occurred, and in which the expulsion of tapeworms marked the disappearance of the symptoms. He also speaks of momentary loss of speech, loss of memory, persistent insomnia, frequent epistaxis, repeated vomiting, disorders of the sexual functions, etc., as occasional symptoms determined by the presence of tapeworm.

Seeger (1852, p. 80) gives the following list of symptoms, with their frequency, considered by him to be of diagnostic value and gathered from the accounts of 100 selected cases of large tapeworms:

Acute colic, 17 per cent; abdominal pains of various sorts, 42 per cent; vertigo, 15 per cent; periodical and habitual headache, usually unilateral, 19 per cent; irregular appetite or bulimia, 31 per cent; frequent nausea, with vomiting or feeling of faintness, 49 per cent; peculiar sensations of movements in the abdomen, 16 per cent; vague pains in different parts of the body, 11 per cent; digestive troubles and irregularities of the bowels, 33 per cent; failure and derangements of speech and special senses, 15 per cent; cerebro-spinal symptoms, especially local or general convulsions (epilepsy, hysteria, melancholia, hypochondria, clonic convulsions, dyspnea, convulsive cough, etc.), 68 per cent.

Hirsch (1879a), in a statistical study of 100 cases of infection with large tapeworms observed by Doctor Mosler in his practice at Giessen and Greifswald, Germany, has given the relative frequency of such symptoms as were considered due to the presence of the parasites.

Of gastro-intestinal phenomena, colic appeared in 14 cases without apparent cause. Abdominal pains of various kinds were present in numerous cases. The prevailing gastric symptoms were, matitudinal vomiting, 1 case; pyrosis, 8 cases; unpleasant eructations after eating, 5 cases; nausea, 13 cases; frequent vomiting, 12 cases; loss of appetite, 6 cases; bulimia, 10 cases, and various sorts of capricious appetites in other cases.

Constipation occurred in 5 cases, diarrhea in 6 cases, and the bowels were irregular in 3 cases.

Epileptiform convulsions, cured after the expulsion of a tapeworm, occurred in one case, and severe manifestations of a convulsive nature were present in 2 cases. Vertigo was complained of in 16 cases. Loss of consciousness occurred in 2 cases. Headache was present in 14 cases. Flickering vision and a sensation of blackness before the eyes were symptoms in 2 cases, and in a third case vision was diminished in one eye. Cardiac palpitation occurred in 6 cases. Salivation was present in 6 cases, anal pruritus in 19 cases, and itching of the nose in 12 cases. Disturbed sleep was common; in 1 case the sleep was much troubled, there was complete insomnia in 1 case, and abnormal sleepiness in a third case.

Of symptoms depending upon general organic disturbances, among others, the following were noticed:



Feeling of weakness, especially in the knees, 2 cases; gradual loss of strength, 4 cases; general and continued weariness, 4 cases; anemia, 1 case; chlorosis, 1 case; paleness without appreciable cause except the presence of tapeworm, 4 cases.

Two cases were marked by icterus, apparently due to tæniasis.

In the actual cases of tapeworm, about 130 in number (the remainder being delusion cases) among the 180 cases observed by Cobbold (1883a), besides gastro-intestinal symptoms, evidences of deranged nutrition, and minor nervous symptoms of common occurrence, severe nervous phenomena appeared several times. Three well-marked cases of chorea occurred in boys (Cobbold's cases X, XI, CXVI) cured after the expulsion of tapeworms. A boy 2½ years old (Case LXXVII) suffering from convulsive fits rapidly improved in health after expulsion of a tapeworm. A little girl (Case CLV) also showed rather severe nervous symptoms. Among adults, partial hemiplegia occurred in 1 case (XXXV), with spectral illusions, and spasms of the muscles of one side of the face, which disappeared after expulsion of tapeworm. Partial reflex paraplegia was present in 1 case (XXXIX) with frequent vertigo and loss of consciousness; after expulsion of tapeworm the worst symptoms disappeared. Locomotor ataxia of upper limbs, with other grave symptoms, 1 case (XXV); locomotor ataxia of lower limbs and muscular twitchings, 1 case (LVIII); partial locomotor ataxia with severe symptoms, 1 case (LXIV). Paraplegia, which almost disappeared after the tapeworm was expelled, 1 case (XCV). Frequent syncope and mental depression, 1 case (XLVIII). There were several other cases in which severe nervous affections occurred, apparently, however, due to other causes, since anthelmintic treatment was without effect upon the symptoms.

It should be noted that most of Cobbold's cases were male adults; Hirsch's cases also were mostly among adults, only 11 patients out of the 100 being under 21 years of age, and only 3 under 10 years, and males were more numerous than females, 74 of the former to 26 of the latter.

Numerous other statistics with regard to tapeworm infection might be quoted, but those given are sufficient to show that severe symptoms are often associated with the presence of the larger tapeworms (especially *Tænia saginata* and *T. solium*), the expulsion of which is followed by the disappearance of symptoms.

#### SYMPTOMATOLOGY AND PATHOLOGY OF HELMINTHIASIS WITH HYMENO- LEPIS NANA.

Owing to the small size of *Hymenolepis nana* one might be led to assume at once that its presence in the human intestine could bring about no harmful effects of importance. On the other hand, a glance

at the evidence furnished by the various cases of *H. nana* on record shows that severe symptoms are of frequent occurrence. As an additional support of the fact that the size of a tapeworm is no index of the amount of damage it may do, a number of instances might be given in which small tapeworms are occasionally even a serious menace to life. In such instances, however, it is usually the case that the number of worms present is so great that mechanical obstruction alone, not to speak of the loss of nutrition to the host, is sufficient to explain the severe results; or it may happen, as occurs in the case of a certain comparatively small tapeworm of the chicken, that the parasites bore deeply into the submucosa and almost or entirely penetrate the intestinal wall, and in this way give rise to very serious effects.

In considering the manner in which *Hymenolepis nana* affects its host, the question of mechanical obstruction may be left out of account, unless the parasite is present in overwhelming numbers when it would be of importance.

Since each worm has a separate point of attachment to the intestine, it is likely that considerable irritation will result if many are present. The rather extensive movements of the larger tapeworms while extending or contracting themselves give rise to a certain amount of irritation, but in the case of *H. nana*, it does not, *a priori*, seem probable that its movements would have much of an irritating effect, unless the worm were present in very large numbers. The assumption that more or less irritation of the intestine is caused by the presence of *H. nana* is supported by the fact that diarrhea and other intestinal derangements, and various reflex symptoms commonly attributed to intestinal irritation, occur frequently. As to the extent of the local effects of the parasite under discussion our knowledge is limited. Although some evidence has been adduced, intended to show that pathological changes occur which are of considerable importance, the balance of evidence seems to indicate that organic changes of the intestine, if occurring at all, are very slight.

Innes (1898) speaks of bloody extravasations found on the mucosa of the ileum which he considers might possibly have marked the points of attachment of the tapeworms (Case No. 3).

According to Grassi (1887d) the worms were found to have bored deeply into the mucosa, and to have caused considerable alteration, but the nature of the change is not specified.

At the post-mortem examination of a case (No. 9) of *Hymenolepis nana*, in which 400 specimens were found in the ileum, Visconti & Segré (1886) noticed that the mucosa throughout the small intestine was tumefied, hyperemic, and covered with a thick layer of grayish mucus, through which the worms were scattered. The greater part of the solitary follicles were tumefied. Microscopic examination of a portion of the ileum showed the mucosa swollen and richly infiltrated

with lymphoid cells. The connective tissue of the submucosa was sclerosed and thickened.

Mingazzini (1899, pp. 598-599, 603) has recently made some observations upon the mode of attachment of *Hymenolepis nana* to the intestine of the rat, which are of interest in this connection. He found that the rostellum in the living state, when the worm is attached to the intestine, is always extruded, and penetrates deeply into the lumen of a gland of Lieberkühn: it may reach as far as the bottom. Only a very slight alteration is produced in the epithelium of the gland, except at the point where the surface of the rostellum and the epithelium are in contact. The hooks on the anterior part of the rostellum penetrate only the epithelial cells, frequently producing some alteration in their shape and contents and occasionally entirely destroying them over a very small area. At the points where the suckers and the epithelium are in contact there are sometimes found little elevations in the latter, corresponding to the cavities of the suckers. Grassi and Calandruccio, after examining the intestines of rats infected with *H. nana*, asserted that at the point of attachment there seemed to be an abnormal number of leucocytes in the connective tissue. Mingazzini, however, found, upon examining the same preparation used by these authors, that the connective tissue of the tunica propria in the region of the point of attachment of the worm was entirely normal as to the number of leucocytes. If *H. nana* acts the same in the human intestine as in that of the rat, it is not possible. Mingazzini believes, to attribute to this cestode the very grave and extensive anatomical changes in the mucosa of the human intestine, which were noticed by Visconti and Segré, and Grassi. The fact that in the great majority of cases of *H. nana* reported, the individuals affected exhibit no phenomena of disturbance, is also considered by Mingazzini an argument against the occurrence of anatomical changes of importance. He believes it is therefore justifiable to consider that the lesions referred to which have been noticed in the human intestine are pathological conditions concomitant with, rather than due to, the presence of the parasite. The nervous phenomena, he adds finally, which sometimes appear in children infected with *H. nana*, and are cured by the elimination of the parasite, are perhaps due to a toxin which, while not altering the structure of the intestine, acts upon the central nervous system.

The toxic effects of intestinal parasites upon their hosts is a question with regard to which little is known, but sufficient work has been done to show that in some instances parasites elaborate substances which are distinctly poisonous when absorbed. In a review of the results of various investigators bearing upon this point, Linstow (1896b, p. 189) expresses the following opinion:

The helminths eliminate a poisonous substance, a toxin or a leucomain, as is the case with the pathogenic micro-organisms and, as in the latter case, it is not the me-



chanical disturbance produced by their presence in the human body, but the toxin, which produces illness, and may cause death. (Translation.)

Vaullegeard (1901) states that the products soluble in water obtained by him from a number of different cestodes contain two sorts of substances, one soluble in alcohol and the other precipitated by it. While no experiments were made with *H. nana*, in the case of *Bothriocephalus punctatus* he was able to demonstrate that the substance soluble in alcohol contained an alkaloid very similar to curarin, while in the substance precipitated by alcohol there was a sort of toxin-ferment which acted upon the nervous centers and disorganized the relations of the nerve cells. In his conclusions he says:

In studying the products contained in different species of worms, we have isolated two toxic substances, one of which acts upon the nervous centers, while the other acts upon the muscles. We are therefore justified in suspecting the importance of these factors in verminous maladies. The critical study of this subject has brought to our attention a large number of symptoms analogous to those provoked by the injection of the toxic substances. \* \* \* Our chemical theory, deduced from our experiments, permits us to understand how good health is possible in spite of the presence of worms. This result should occur whenever the excretion eliminates a quantity [of the toxic materials] equal to the absorption, for in this case the dose contained in the organism is not sufficiently active. The troubles correspond to the accumulation of toxic products; one readily comprehends that when some morbid influence becomes effective, it may determine the appearance of symptoms due to worms, which had been present for a long time without manifesting themselves. (Translation.)

In the case of *H. nana* it seems probable that the elimination of toxic materials which are absorbed by the host is one of the most important factors in the etiology of symptoms. Upon this point Linstow (1896b, pp. 190-191), after reviewing shortly the symptoms which have been attributed to the parasite, remarks:

That such a minutely small, delicate animal can not produce these serious disturbances through mechanical irritation, perhaps does not need the proof that its virulence must be very intense. (Translation.)

The analysis of the symptoms reported in the various cases of *Hymenolepis nana* is complicated by a number of circumstances. Among others, the question arises as to whether the phenomena exhibited were due to helminthiasis, or to other causes; this question is more or less definitely decided in some instances by the effect of anthelmintic treatment. Again, in those cases in which there was a multiple infection, to what extent did *Hymenolepis nana* influence the symptoms and how much are the other parasites to be blamed? This is a question which can not be answered with certainty, but if the other parasites are comparatively few in number, as manifested by the number of eggs in the feces or by the number of worms passed after treatment, and are of kinds which do not usually cause much trouble, or if the symptoms disappear and recur after successive treatments in correspondence with the recurrence in the feces of the eggs of *H. nana*, we may assume that it is by the latter parasite that the symptoms are chiefly determined.



The presence or absence of symptoms<sup>a</sup> has been noted in more or less detail in 49 out of the 101<sup>b</sup> cases.

Of the 49 cases, 3 (Nos. 54, 57, 89) showed no symptoms whatever which could be traced to *H. nana*. It is only very remotely possible that there was any connection between the presence of *H. nana* in cases 1 and 3 and the diseases mentioned in these two instances, viz, meningitis and anemia, fatal in both cases. In 9 other cases (Nos. 10, 11, 13, 14, 15, 35, 53, 86, 101) the symptoms were only slight. In case 35, although thousands of *H. nana* were present, there were no symptoms of any kind exhibited, with the exception of occasional slight abdominal pains. Although several hundred specimens, besides numerous *Oxyuris* were passed after successive treatments in case No. 53, the patient was healthy in every respect and showed no symptoms except an itching of the nose. In 4 cases (Nos. 6, 47, 82, 97) the severity of the symptoms is not defined (in Nos. 82 and 97, however, they were probably slight). The symptoms in the 31 cases remaining are more or less severe. Only 17 of them, however (Nos. 7, 8, 32, 33, 34, 36, 37, 38, 39, 41, 42, 43, 44, 49, 81, 94, 95), are marked by symptoms in which the influence of *Hymenolepis nana* can be definitely traced, either by the disappearance or improvement of the symptoms after the expulsion of *H. nana* in those cases in which there seemed to be no other parasites present, or, if present, few in number compared with *H. nana*; or by the correspondence between the reappearance of *Hymenolepis* eggs in the feces after treatment, and the recurrence of symptoms.

In 13 (Nos. 7, 8, 32, 33, 34, 37, 38, 39, 42, 43, 49, 94, 95) of these 17 cases, some disorder of the digestive system was noted. The relative frequency of symptoms referable to the digestive system is as follows:

Bulimia or increased appetite, 3 cases (Nos. 7, 8, 39).

Perversion of appetite, 1 case (No. 95).

Gastric dyspepsia and difficult digestion, 1 case (No. 38).

Functional gastro-intestinal disorders, 1 case (No. 37).

Frequent vomiting, 1 case (No. 49).

Abdominal pain or paresthesia, 11 cases (Nos. 7, 8, 33, 34, 37, 38, 39, 42, 43, 49, 94). In one of these cases (No. 38) there was a sensation of crawling in the abdomen, and heat in the epigastrium; in another (No. 43) pain, and crawling and gnawing sensations; in another case (No. 42) pain and a sense of pressure; it was noted in one case

<sup>a</sup>This is leaving out of consideration the symptoms in cases Nos. 51 and 52, not available to me on account of the Russian text in which they were recorded, and also the symptoms which may have been mentioned by Venuti (1895) in connection with his 23 cases, but his paper, unfortunately, is not at present accessible.

<sup>b</sup>The list of symptoms was compiled before the discovery of cases 102 to 106, which are therefore not included in the discussion. The ward records of these five cases showed, however, no symptoms which could be traced to the presence of the parasites.

(No. 39) that the pain in the epigastrium increased on palpation: in 2 cases (Nos. 33, 34) the pains were frequent.

Diarrhea, 3 cases (Nos. 49, 94, 95). In one case (No. 49) the diarrhea was lienteric in nature and of long standing, and in a second case (No. 95) it had persisted continually for two years.

Diarrhea alternating with constipation, 2 cases (Nos. 33, 34).

Severe intestinal troubles, 1 case (No. 32).

Nervous symptoms were noted in 15 cases (Nos. 7, 8, 33, 34, 36, 38, 39, 41, 42, 43, 44, 49, 81, 94, 95). In 11 of these cases convulsions or spasms occurred.

Epileptiform convulsions, 7 cases (Nos. 7, 8, 33, 34, 36, 38, 39). Of these, 3 were reported cured after treatment, while in the others the symptoms disappeared for some time after treatment but later recurred, and in 2 (Nos. 33, 34) of these latter there was no corresponding reappearance of eggs in the feces when the symptoms recurred after having ceased for several months.

Choreic convulsions, 1 case (No. 42).

Clonic spasms of extremities, 2 cases (Nos. 41, 43).

Nodding spasm of head, 1 case (No. 49). This symptom was improved but not cured after the expulsion of *H. nana*.

Diffuse tremor of frequent occurrence, 1 case (No. 38).

Paralysis or paresis was seen a number of times.

Weakness of right side of body, 2 cases (Nos. 41, 43).

Distortion of mouth, 2 cases (Nos. 41, 43).

Strabismus and diplopia, 6 cases (Nos. 39, 40, 41, 42, 43, 49). In 1 of these cases (No. 41) the strabismus was not cured and showed only very slight signs of improvement after anthelmintic treatment.

Difficult speech, 3 cases (Nos. 41, 42, 43).

A number of other so-called reflex symptoms were encountered.

Vertigo, 1 case (No. 44).

Headache, 5 cases (Nos. 39, 41, 43, 44, 49).

Nasal pruritus, 1 case (No. 49).

Numbness in lumbar region, 1 case (No. 44).

Diminished vision, 1 case (No. 42).

Mental symptoms, 5 cases. Two cases (Nos. 38, 43) were melancholy, taciturn, stupid; in 2 others (Nos. 7, 8) there were melancholia, indolence, and weakening of the mental faculties; 1 case (No. 49) was drowsy.

Respiratory disorders, 4 cases. Dyspnea occurred in 2 cases (Nos. 37, 48), in one of which it had been continual during two years, and was cured immediately after the expulsion of *H. nana*; in 1 case (No. 38), a scrofulous subject, there was a rough, diffuse, vesicular murmur of the lungs, whether cured after anthelmintic treatment is not stated; and in 1 case (No. 41) there was an occasional dry spasmodic cough.

Nocturnal enuresis, 1 case (No. 81).

Cardiac palpitation, 1 case (No. 39).

Shivering, grinding of teeth, biting of lips, 1 case (No. 49).

Pupils unequal, but reacting to light, 1 case (No. 42).

Fever, 3 cases. In 1 case (No. 49) there was said to be some fever; in 2 cases (No. 94, 95) the fever was irregular and intermittent, in 1 of which it appeared at intervals for two years.

Restless sleep, 1 case (No. 94).

Somnambulism, 1 case (No. 38).

Occasional remark is made as to the general appearance; usually the nutrition does not seem to be much affected.

Emaciation, 1 case (No. 49).

Paleness, 4 cases (No. 39, 42, 43, 49).

Weak, delicate, scrofulous, 1 case (No. 38).

With regard to the phenomena exhibited by the remaining cases in which symptoms were noticed, there is no way of demonstrating whether the presence of *Hymenolepis nana* was anything more than an attendant circumstance, indeed, in many of the cases it is quite apparent that there could have been no causal relation between the presence of the tapeworm and the symptoms, while in others, in which such a connection seems more or less probable, the evidence is too incomplete to warrant such an assumption, and in a number of these latter it is furthermore questionable whether the other parasites present might not be of equal or greater importance in the etiology of symptoms. Following is a list of symptoms, with their frequency, taken from all the reports of cases in which symptoms were noted, without regard to questions of etiology:

Disorders of the digestive system occurred in 28 cases.

Diarrhea, 9 cases.

Diarrhea, alternating with constipation, 2 cases.

Constipation, 1 case.

Diminished appetite, 3 cases.

Increased appetite, 4 cases.

Capricious appetite, 2 cases.

Perverted appetite, 2 cases.

Vomiting, 3 cases.

Abdominal pain or paresthesia, 16 cases.

Thirty-three cases were marked by symptoms connected with the nervous system; in 11 of these cases the nervous symptoms were only slight. A number of symptoms occurred as follows:

Epileptiform convulsions, 9 cases.

Choreic convulsions, 1 case.

Clonic spasms of extremities, 2 cases.

Nodding spasm, 1 case.

Frequent, diffuse tremor, 1 case.

Sinistral hemiparesia, 1 case.

Weakness of right side, 2 cases.

Ataxia and weakness of legs, 1 case.

Strabismus and diplopia, 6 cases.

Nystagmus, 1 case.

Disturbed vision, 1 case.

Diminished vision, 1 case.

Headache, 10 cases.

Disturbed sleep, 3 cases.

Fever, 7 cases.

Vertigo, 2 cases.

Difficult speech, 3 cases.

Mental symptoms, 7 cases.

Nasal pruritus, 3 cases.

Formication of body, 2 cases.

Numbness of lumbar region, 1 case.

Nocturnal enuresis, 1 case.

Cardiac palpitation, 2 cases.

Shivering, grinding of teeth, biting of lips, 1 case.

Of other phenomena not directly connected either with the digestive or nervous systems the following may be noted:

Chyluria, 1 case (No. 87). The doubtful connection of *Hymenolepis* with this case has already been remarked above in the discussion of the case.

Slight eosinophilia, 1 case (No. 82). So far as I have found, this case is the only one in which the results of a blood examination were reported.

Paleness, 13 cases.

Emaciation, 4 cases.

With regard to the symptoms which have been enumerated it will be noticed that there are no essential peculiarities to distinguish them from the symptoms found with the larger tapeworms (*Tænia*). In character the symptoms are similar in both instances, being remarkable chiefly on account of their variety and lack of uniformity.

According to the manner in which the cases are selected, a variety of results regarding the frequency of symptoms may be obtained from a comparison of *H. nana* with other tapeworms.

The cases of *H. nana* which showed severe nervous symptoms—taking into consideration all such cases without regard to the probability that in many of them the symptoms were due entirely to other causes than the presence of the parasite—form 45 per cent of the 49 cases in which the presence or absence of symptoms was distinctly referred to, and 21 per cent of the entire number.<sup>a</sup> Seeger's table (see p. 66) gives the percentage of severe nervous symptoms occurring in 100 cases of tapeworm as 68. Seeger, however, in making up his statistics, apparently has used only such cases as exhibited definite

<sup>a</sup>See footnotes, p. 71.



symptoms, and, moreover, has not given due consideration to possible causes of the symptoms other than the presence of *Tænia*. A comparison between the 49 cases of *H. nana* referred to and Seeger's cases is, nevertheless, not unwarranted. Not only in the latter as in the former is no attention paid to possible causes in the etiology of symptoms other than the presence of tapeworm, but they are in a sense selected cases. Seeger's cases were selected because of the occurrence of symptoms, and similarly, in connection with the cases of *H. nana* just mentioned, there has been a sort of selection, namely: If symptoms had not occurred in nearly all of these cases the circumstance of infection with *H. nana* would not have been discovered; these cases were thus picked out automatically from among probably a large number of cases, the remainder of which were without symptoms and thus never came under observation.

Severe nervous symptoms, apparently determined by the presence of tapeworm, were present in at least 10 per cent of Cobbold's cases (see p. 67). Convulsions were present in only 3 per cent of Hirsch's cases (see p. 66), but other phenomena occurred in a considerable number which will allow an estimate of severe nervous symptoms in about 10 per cent of the cases. Not more than 12 to 15 per cent of all<sup>a</sup> the cases of *H. nana*, or 30 per cent of the cases in which the presence or absence of symptoms has been definitely reported, exhibited severe nervous symptoms attributable with any degree of certainty to the action of the parasite.

A comparison with Seeger's statistics tends to show that severe symptoms are less common in cases of *H. nana* than in cases of other tapeworms, while comparison with the statistics of Cobbold and Hirsch indicates that grave nervous disturbances are more common in cases of *H. nana* than in cases of other tapeworms. All of these comparisons are open to criticism, but the first, although perhaps the most artificial of the three, probably arrives nearer the truth than either of the others, and it may be affirmed that severe effects from the presence of *Hymenolepis nana* are no more common than from the presence of other tapeworms, but on the contrary are very likely much less common. The high percentage of severe effects with cases of *H. nana* as compared with cases of other tapeworms is no doubt due, in part at least, to the fact that a proportionately greater number of cases of *H. nana* pass unnoticed than of larger tapeworms. The presence of a large tapeworm is usually made manifest, sooner or later, by the passage of segments, while a microscopic examination is necessary to determine the presence of *H. nana*, and, as already remarked, unless there happen to be symptoms which will bring the patient under medical observation, in which case a fecal examination may be made, the chances are very much against the diagnosis of any particular case among the

<sup>a</sup>See footnotes, p. 71.

general population. Thus it has happened that a comparatively large number of cases have presented themselves in which severe symptoms were associated with the occurrence of *Hymenolepis nana*, while probably a very large number of cases have never been noticed because there have been no symptoms. A case of *Tænia saginata* or *T. solium*, on the other hand, is very likely to come under observation; the average individual, when he has once observed the passage of worms from his intestine, usually does not delay, whether there are any other unpleasant symptoms or not, to seek relief from the presence of his unwelcome guests: the case consequently stands a very good chance of being placed somewhere on record. Another point might be noticed in this connection. *Hymenolepis nana* is more especially a parasite of children; the larger tapeworms are more common among adults. It is rather to be expected that children would, in general, experience more severe effects from parasitic infection than adults: for example, nearly half of Cobbold's cases (as noted above), which exhibited severe nervous symptoms, were children, while the great majority of all his cases were adults: an indiscriminate comparison of statistics, therefore, without taking into account the question of age of affected individuals, is not likely to give a true idea of the relative nocuity of the different parasites.

The symptomatology of helminthiasis with *Hymenolepis nana* may be summed up as follows:

The effects of helminthiasis with *H. nana* are no more severe than may occur from infection with other tapeworms, nor, if it is considered that many cases of the former are probably overlooked, are serious symptoms more common. Although the effects are usually so slight, even when the parasite is present in considerable numbers, that the symptoms are only very mild or absent entirely, it occasionally happens, as with the larger tapeworms, that severe symptoms (persistent diarrhea, epileptiform attacks, etc.) are exhibited. The most frequent symptoms determined by the presence of *H. nana* are abdominal pain, which may or may not be associated with diarrhea; convulsions of various sorts, frequently epileptiform; headache and strabismus. Nasal or anal pruritus, common in cases of infection with other tapeworms, is rarely seen with *H. nana*. In many cases in which a neuropathic condition is already present, infection with *Hymenolepis nana* is likely to result in an aggravation of the morbose phenomena, and, in general, a predisposition to nervous disease seems to be the important factor in the appearance of nervous symptoms.

#### DIAGNOSIS.

In speaking of the diagnosis of helminthiasis, Blanchard (1891a, p. 100) remarks as follows:

The persistence of digestive troubles and the diversity and irregularity of other symptoms are very suggestive of helminthiasis. The diagnosis is rendered more

probable when the patients are children. Intestinal parasites, in fact, play a considerable part in the production of infantile maladies, a circumstance which is systematically disregarded by a great many physicians. When helminthiasis is once suspected, one ought to determine as nearly as possible to what species the offending parasite belongs. Success in treatment depends upon this point; a remedy which is sure in its effects upon one species may be useless against other worms. Entire worms or fragments which have spontaneously quitted the intestine may be found in the dejecta. A careful examination of these furnishes valuable data with regard to the treatment to be pursued, but one ought not to limit one's self to such a superficial means of determination. Since it frequently happens that several parasites live side by side in the intestine of the same individual, it is indispensable, especially in grave cases, to make a more careful examination of the feces, in order to determine exactly what different species may be harbored by the patient. This examination presents no difficulties, and only requires a little patience, since all the eggs are not equally easy to distinguish. The egg of each species of parasite, however, has a very characteristic shape and size, which renders the diagnosis very easy. (Translation.)

To make the examination it is necessary simply to rub up with a drop of distilled water on a glass slide, a very small particle of the feces to be examined, cover with a cover glass, and examine with a moderately high power, a Zeiss 4 or 8 mm., Leitz 5 or 7, Bausch and Lomb one-half or one-fourth, or other equivalent objective. Some care is requisite in looking for the eggs of *H. nana*, otherwise they are very liable to be passed unperceived, because of their great transparency. The presence of three pairs of hooks on the embryo contained within an egg indicates that it is a cestode egg, while the presence also of two distinct membranes, an inner one closely investing the embryo, and an outer separated from the inner by a considerable intervening distance, is characteristic of *Hymenolepis* eggs. The shell of the egg of *Tænia saginata* or of *T. solium* is thick, radially striated, and lies closely against the embryo. The outer membrane of the egg of *Hymenolepis diminuta* may likewise be radially striated, a character, which when present will distinguish it from *Hymenolepis nana*. The substance intermediate between the outer and inner membranes is more prominent in *H. diminuta*, and there are no filaments attached to the poles of the inner membrane as in *H. nana*. The presence of polar papillæ on the inner membrane is a characteristic feature of *Hymenolepis* eggs not always readily apparent. The filaments in the egg of *H. nana* are often difficult to distinguish, but in case they are not seen at once, careful observation of a number of specimens, especially if an immersion lens be used, will usually reveal them.

Charcot-Robin crystals, which were found by Leichtenstern (1892) almost constantly present in the feces of patients with helminthiasis, have not been found in cases of *Hymenolepis nana*.

It is doubtful whether the spherical bodies described by Senna and referred to above (p. 33) can be considered of diagnostic importance. As already remarked, Senna at first considered these bodies to be eggs in course of development, but since he found them not only in feces



which contained eggs of *H. nana*, but also in feces in which the presence of eggs could not be established, he was inclined to discard his former interpretation. It is possible, in those cases in which the spherical bodies but no eggs were present, that there were in reality worms in the intestine, which, however, had not attained their full growth; consequently the eggs had only partially developed and were found in the feces only in their immature stages.

#### TREATMENT.

Male fern is the only remedy which has met with any degree of success in the treatment of *Hymenolepis nana*. Kouso, kamala, santonin, thymol, or pomegranate proved ineffective in the cases in which any of these were tried (Nos. 4, 5, 7, 8, 38, 43, 48, 53, 89).

The usual precautions should be taken in the treatment with male fern, namely, taking care to have the patient in the best possible physical condition, and preceding the administration of the tæniacide by a preparatory treatment of mild laxatives and a light diet in which the amount of starchy foods is reduced to a minimum (Eichhorst, 1901a, p. 298). In the technic of tapeworm treatment some authors recommend a salad of dried herring, garlic, and onions, the evening before the administration of the male fern; this procedure was followed in a number of cases of *Hymenolepis nana*, but to what advantage does not appear. The preparation of male fern to be employed is the official oleo-resin (Oleo-resina aspidii, U. S. P.), or ethereal extract of European pharmacy, which must be fresh to be effective. The dose for adults is 2 to 4 cc. (fl. ʒ ss.-j). There is some danger attending its use; a number of cases are on record in which poisoning occurred, several resulting fatally. Six drams and even less have caused death. The symptoms of poisoning were vomiting, vertigo, headache, diarrhea, severe pains in the abdomen, dyspnea, cold sweat, coma, convulsions, mania, and temporary or permanent blindness.

After the preliminary treatment the male fern is given in the morning upon an empty stomach. In its administration various methods have been used: it has been given in pills, mucilage, syrup, electuary with calomel, etc. Eichhorst (1901a, p. 299) has obtained satisfactory results with gelatin capsules. A number of small doses at intervals, or one, two, or three larger doses, may be given; Mertens (1892) found the latter procedure preferable.

One treatment may not suffice for a cure; in at least 20 of the cases of *H. nana* the eggs were found in the feces after treatment, usually after an interval of about fifteen days, and in several instances 4 or 5 repetitions of the treatment were necessary.



## PROPHYLAXIS.

Upon the assumption that *H. nana* of man is the same form as *H. murina* of the rat, and that development occurs in man in the manner demonstrated by Grassi for the rat, namely, without a change of hosts, the prophylactic precautions to be observed are evident.

As far as possible banish rats and mice from the premises, and keep food out of their reach, especially food that is eaten raw, or after cooking is kept for some time before being eaten.

Considering also the possibility that some insect may act as an intermediate host, insects should, on this account, as well as for esthetic and general hygienic reasons, be kept out of the food.

Of course not only food, but other objects which have been contaminated by the feces of rats or mice, or of an infected person, may convey infection by carrying the eggs to the mouth; hence, articles (including fingers) which are placed in the mouth should be clean, and unnecessary objects should be kept out of the mouth; this rule, which is applicable also in a scheme of prophylaxis against parasitic infection in general, should be enforced, especially in the case of children, who are notoriously indiscreet with regard to what they put in their mouths, and in view of the possibility mentioned in the foregoing paragraph, special care might well be taken that they do not, accidentally or willfully, put in the mouth and swallow insects. The feces of infected persons should be properly disposed of.

Blanchard (1891a, p. 105) epitomizes the subject of prophylaxis in the following words:

From whatever point of view examined, the great problem of the suppression of parasitic diseases, whether they be infectious or not, is summed up in this formula: Cleanliness, always cleanliness.<sup>a</sup>

The Flavopunctate Tapeworm—*HYMENOLEPIS DIMINUTA* (Rudolphi, 1819)  
Blanchard, 1891.

## HISTORICAL REVIEW.

The original description<sup>b</sup> of the species *Hymenolepis diminuta* was given by Rudolphi (1819, pp. 689–690) as follows:

<sup>a</sup> A quelque point de vue qu'on l'examine, le grand problème de la suppression des maladies parasitaires, qu'elles soient ou non infectieuses, se résume donc en cette formule: de la propreté, encore de la propreté.

<sup>b</sup> *Tenia diminuta* R. n. sp.—T. capite obconico, collo longo, tenui; articulis anticis bevissimis [sic], reliquis subcuneatis obtusis. *Hab.* In intestinis *Muris ratti* gravidi Olfers in Brasilia reperit.

Specimina sex ad novem pollices et quod excurrit longa, nam fragmentis computatis forsan longiora. *Caput* obconicum, *oculis* anticis majusculis, exacte T. omphalodis, quam Mantiss, p. 491, descripsi, sed multo minus, unde nomen triviale desumsi. *Collum* longum tenue. *Articuli* priores rugæformes, sensim majores, semper tamen longitudinis ratione habita breves, angulis obtusis; posteriores passim irregulares, sed breves. *Ora* subglobosa, mediocria.

*Obs.* Omphalodem dixerim, nisi caput multo minus, ova major forent; hæc forsan in Omphalode crescere posse contenderes, sed caput non augebitur.

*Tænia diminuta* R. n. sp.—*Tænia*: Head obconical; neck long, slender; anterior segments very short; the rest, subcuneate, obtuse.

*Habitat*.—Collected by Olfers in Brazil from the intestines of a gravid rat (*Mus rattus*). Specimens 6 to 9 inches or more in length, and, since the measurements were taken from fragments, perhaps longer. Head obconical, with rather large suckers situated anteriorly; it is similar to that of *T. omphalodes* (described, Mantissa [Rudolphi, 1819], p. 491), but much smaller, for which reason I have chosen the specific name [*diminuta*]. Neck long and slender. Segments at first resembling corrugations, gradually becoming larger, with their length always remaining less than their width, with obtuse angles; posterior segments more or less variable, but short. Eggs subglobose, of medium size.

NOTE.—I would have said it were *omphalodes* if the head were not much smaller and the eggs larger; the contention might be made that the eggs of *omphalodes* could grow larger; a head, however, will not increase in size. (Translation).

Some years later Creplin (1825a, pp. 71–72) described as a new species a tapeworm from the rat which he named *Tænia leptocéphala*. The following is translated from his description:<sup>a</sup>

*Tænia*: Head slender; suckers large, globose; rostellum, conical, truncated, unarmed; neck, continuous, elongated; segments all short.

*Habitat*.—I once collected, April 19, 1822, two specimens of this tapeworm in the intestines of a mouse (*Mus musculus*). Of these I took out only one with a head, and a fragment of the posterior part of the body.

I am compelled to give a description from these specimens as already preserved for some time in alcohol, since I did not have time to examine them when they were fresh.

The length of the worm with the head equals 10 to 11 inches; of the other without a head about 9. The width, decreasing from the tail toward the head, measures a little more than a line at its maximum in the posterior part of the body. Color white.

Head small, slender, furnished with large globose suckers, which when projecting have orbicular apertures, likewise large, and with a rostellum, conical, truncated, and unarmed. With the suckers withdrawn the length of the head equals its thickness at the base. Neck rather long, slender, continuous with the head, flattened. Anterior segments resembling corrugations; following segments very short,

<sup>a</sup> T. capite tenui, oculis maximis globosis, rostello conico truncato inermi, collo continuo elongato, articulis omnibus brevibus.

*Hab.* Semel (d. 19. Apr. 1822) in int. *Muris musculi* offendi hujus Tæniæ duo specimina, quorum alterum solum cum capite extraxi, et fragmentum corporis postici.

*Descriptionem* dare coactus sum de speciminibus illis jam per quoddam tempus in spiritu vini servatis, cum recentium examinandorum tempus deficeret.

*Longitudo* vermis capite adhuc gaudentis æquat decem ad undecim pollices, alterius capite privi novem circiter. *Latitudo*, a cauda ad caput semper decrescens, maxima, postica in parte lineam parum excedit. *Color* albus.

*Caput* parvum, tenue, *osculis* vero magnis, globosis, apertura orbiculari pariter magna, exstantibus, et *rostello* caput ipsum longitudine et basi sua etiam crassitie (*osculis* deductis) æquante, conico, truncato, inermi instructum. *Collum* satis longum, subtile, cum capite continuum, planum. *Articuli* antichi rugæformes, sequentes brevissimi, marginibus lateralibus obtusis, reliqui omnes, semper breves, anticam partem paululum contractam, margines laterales interdum convexiusculos, interdum fere rectos, marginem posteriorem vero tumidulum exhibent. Ultimi articuli non adsunt. Foramina articularum non vidi.

with obtuse lateral margins; all the rest, always short, present an anterior portion somewhat contracted, lateral margins sometimes slightly convex, sometimes almost straight, and a swollen posterior margin. Final segments not present. Openings of the segments not seen. (Translation.)

Dujardin (1845a, p. 579, pl. 12, fig. G) enlarged upon Creplin's account of the species *Tænia leptcephala*, adding sufficient detail to furnish a fairly complete description, and moreover recognized the apparent identity of Creplin's species and *Tænia diminuta* of Rudolphi. As translated his account reads as follows:

*Tænia leptcephala*.<sup>a</sup>—From 100 to 500 mm. long, from 1.5 mm. to 4 mm. broad, composed of very numerous and very short segments four to nine times as broad as long; head almost globular, from 0.26 mm. to 0.30 mm. broad, may lengthen itself by means of a conical, unarmed rostellum, sometimes very slender; suckers deep with very salient edge, 0.16 mm. broad; first segments very short, the following ones (male) six to nine times as long as broad; genital orifices unilateral; penis smooth, filiform; eggs almost globular with three envelopes; the outermost smooth at first, then finally granular, from 0.062 mm. to 0.074 mm. long; the middle one membranous; the innermost somewhat quadrangular, rounded, from 0.041 mm. to 0.042 mm. long; embryo from 0.032 mm. to 0.036 mm. with hooks from 0.015 mm. to 0.017 mm.

<sup>a</sup> *Ténia leptocéphale* (*Tænia leptcephala*).—Long de 100 à 500 mm., large de 1 mm. 5 à 4 mm., formé d'articles très nombreux et très courts, quatre à neuf fois aussi larges que longs; tête presque globuleuse, large de 0 mm. 26 à 0 mm. 30, pouvant se prolonger en une trompe conique, inerme, quelquefois très mince; ventouses profondes à bord très saillant, larges de 0 mm. 16; premiers articles très courts, les suivants (mâles) six à neuf fois aussi longs que larges; orifices génitaux unilatéraux; pénis lisses, filiformes; œufs presque globuleux à trois enveloppes; l'externe lisse d'abord, puis finement granuleuse, longue de 0 mm. 062 de 0 mm. 074; la moyenne membraneuse; l'interne un peu quadrangulaire, arrondie, longue de 0 mm. 041 à 0 mm. 042; embryon de 0 mm. 032 à 0 mm. 036 avec des crochets de 0 mm. 015 à 0 mm. 017.

Sous ce nom, donné par M. Creplin à un ténia incomplètement décrit, je réunis plusieurs ténias dont il faudra peut-être faire deux ou trois espèces; savoir: 1° un ténia long de 520 mm., large de 4 mm. en arrière, avec la tête de 0 mm. 285, trouvé dans un rat (*Mus rattus*) à Rennes, ses pénis ou lemnisques sont larges de 0 mm. 019, saillants de 0 mm. 06, ses testicules sont flexueux et non pelotonnés et ne s'avancent pas au-delà du milieu de chaque article; ses œufs ont l'enveloppe externe elliptique longue de 0 mm. 066 à 0 mm. 074; 2° plusieurs ténias trouvés à Rennes dans des surmulots (*Mus decumanus*) ayant la tête large de 0 mm. 24 à 0 mm. 26, les pénis peu saillants, larges de 0 mm. 016, et les testicules repliés et pelotonnés dans presque toute la largeur des articles mâles; les œufs presque globuleux sont longs de 0 mm. 068; 3° fragments de ténia longs de 100 à 200 mm. provenant d'un autre surmulot, et remarquables par leurs pénis très longs, filiformes, larges de 0 mm. 028; les derniers articles larges de 2 mm. 2 sont longs de 0 mm. 75 et contiennent des œufs ronds larges de 0 mm. 068; 4° des ténias longs de plus de 150 mm., sans tête, trouvés dans deux mulots (*Mus sylvaticus*) à Rennes; ils sont larges de 0 mm. 7 en avant et de 4 mm. 5 à 5 mm. en arrière, où les derniers articles remplis d'œufs sont dix à quinze fois aussi larges que longs; les articles intermédiaires mâles ont le réceptacle du pénis en forme de massue, ils laissent sortir des spermatozoïdes filiformes très-longs, mais je n'ai pas vu de pénis saillant; les œufs sont globuleux, larges de 0 mm. 062 à 0 mm. 07, mais plus ordinairement de 0 mm. 065; leur coque est granuleuse (voyez Atlas, pl. 12).—Il faut, je crois, rapporter à la même espèce celle que Rudolphi nomme *Tænia diminuta*.



Under this name, given by M. Creplin to an incompletely described tapeworm, I include several tapeworms which will perhaps have to be subdivided into two or

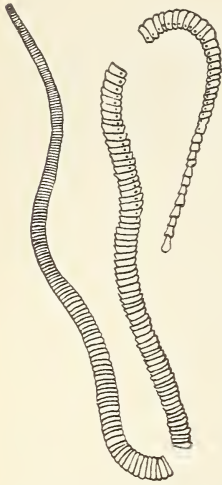


FIG. 68.—Strobila of *H. diminuta*. Natural size. (After Weinland, 1861, pl. 4, fig. 10, from Leuckart, 1863, p. 398, fig. 116.)

three species, namely: First, a tapeworm 520 mm. long, 4 mm. broad in the posterior portion, with a head 0.285 mm. [broad], found in a rat (*Mus rattus*) at Rennes; its penes, or lemnisci, are 0.019 mm. broad, projecting 0.06 mm.; its testicles [probably misinterpretation of seminal vesicle and receptacle] are flexuous and not conglobate, and do not project beyond the middle of each segment; the external envelope of its eggs is elliptical, from 0.066 mm. to 0.074 mm. long; second, several tapeworms found at Rennes in brown rats (*Mus decumanus*) with a head from 0.24 mm. to 0.26 mm. broad, the penis not very salient, 0.016 mm. broad, and the testicles [probably misinterpretation of seminal vesicle and receptacle] folded and conglobate, throughout almost the whole breadth of the male segments; the eggs, almost globular, are 0.068 mm. long; third, fragments of tapeworm from 100 to 200 mm. long, coming from another brown rat, and remarkable because of their very long filiform penis, 0.028 mm. broad; the last segments, 2.2 mm. broad, are 0.75 mm. long, and contain round eggs 0.068 mm. broad; fourth, tapeworms more than 150 mm. long, without a head, found in two field mice (*Mus sylvaticus*) at Rennes; they are 0.7 mm. broad in the anterior portion and from 4.5 mm. to 5 mm. in the posterior portion, where the last segments, filled with eggs, are ten to fifteen

times as broad as long, the receptacle of the penis in these intermediate male segments is club-shaped; these segments send out very long filiform spermatozoa, but I did not see a salient penis; the eggs are globular, from 0.062 mm. to 0.07 mm. broad, but more commonly 0.065 mm. broad; their shell is granular (see Atlas, pl. 12). I think we should refer to the same species that which Rudolphi calls *Tenia diminuta*. (Translation.)

Weinland (1858) was the first to report the occurrence of *Hymenolepis diminuta* in man; he described it as a new species, *Hymenolepis flavopunctata*, in the following words (see also p. 98):

The length of the whole worm is between 200 and 300 mm., that is, from 8 to 12 inches. There were pieces of 50 mm. in length, consisting of very young joints, only one-fifth mm. long and 1 to 1½ mm. broad; again, other pieces, about 100 mm. long, consisting in their anterior half of white, immature joints, one-third to one-half mm. long, and 1½ to 2 mm. broad, while the mature joints of the posterior half, which are of a grayish tint (produced by the eggs which they contain), average 1 mm. in length and 1½ to 2 in breadth. In the young joints the sides form straight lines, the transverse diameter being equal throughout the joint; in the riper ones they are round and bulged, and the transverse diameter is the greatest in the midst of each joint. One of the pieces, which is especially mentioned in the catalogue of Dr. J. B. S. Jackson, shows the form of the joints when fully matured and soon to be freed as proglottides. They are in this specimen

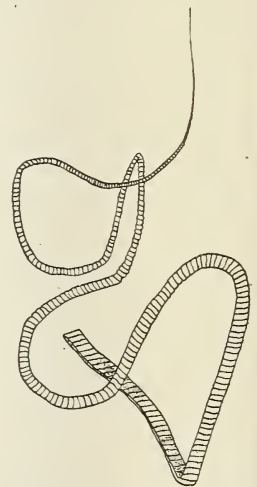


FIG. 69.—Strobila of *H. diminuta*. Natural size. (After E. Parona, 1884, fig. 1.)



triangular in shape, being narrow in front and suddenly broadening behind, evidently having already discharged the eggs from the anterior part of the joint, while generally proglottides deposit their eggs only after they are free. In other specimens these last joints, being yet quite full of eggs, are more oblong, even with the transverse diameter longer than the longitudinal. In either case the proglottides are very loosely connected with each other. In relation to the genital organs, we have mentioned above the yellowish spot lying near the middle line in the anterior part of each joint, and it is for this we have called the species *flavopunctata*.

These spots are the testicles [seminal receptacle, see p. 89], appearing under the microscope as a globular gland, with another smaller one attached to it; this latter one runs out, toward the side of the joint, into a long, slender canal, in which lies the penis. The genital openings are situated all on one and the same side of the worm, while in all true *Tænia*s (see p. 51, note) known thus far, they are found irregularly, now on one, now on the other side. The configuration of the uterus, also, differs greatly from that in the genuine *Tænia*s. There is no main stem in the midst with lateral branches, as in the latter; but, on the contrary, the eggs are crowded over the whole joint. It sometimes appears as if they were arranged in straight lines along the joint; but this is certainly owing only to the regular lines of muscular contractions. Only fresh specimens can decide ultimately the structure of the uterus. From a careful dissection of the younger joints, we should judge that it consists of globular blind sacs, located here and there in the joint, and connected by fine tubes terminating finally in the vagina. The most characteristic feature in this worm is its eggs, the number of which may be counted by thousands in each ripe joint. They are very large, measuring 0.054 mm. in diameter, and under a low power of the microscope appear as transparent balls with a yellow dot in them. With a higher power, we easily distinguish three distinct eggshells (figs. 9, 1, a, b, c). The

outside shell is translucent, elastic, cracking in sharp angles under pressure, and only 0.0007 mm. thick; this shell is folded by application of glycerin. The second shell is membranaceous and irregularly wrinkled, thinner than the first, and immediately attached to it. This second shell, showing through the first, gives to the whole sur-

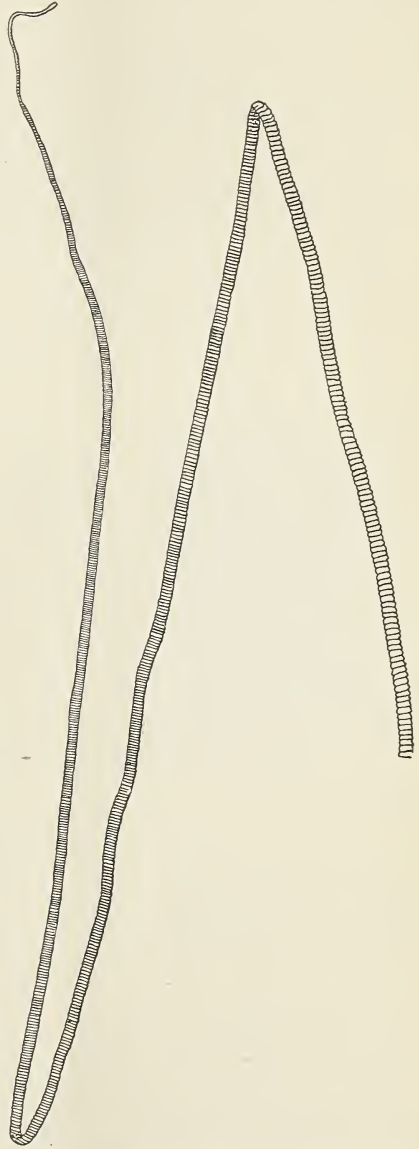


FIG. 70.—*Hymenolepis diminuta*. Natural size.  
(After Grassi, 1888 1, pl. 11, fig. 1.)

face of the egg a wrinkled appearance, though the first shell is in reality entirely smooth. The large cavity which is formed by these two outside shells contains a fluid (this fluid, which has the appearance of albumen, turns milk white when brought into contact with water. Such an albuminous fluid between the two eggshells has also been noticed by Dujardin in the eggs of a Tænioid from *Fringilla domestica*, L.), in which swims the small globular embryo (measuring only 0.024 mm.), inclosed in a third shell, closely attached to it, but of considerable thickness (0.001 mm.). We can not state with certainty that there are three pairs of spines to this embryo; if there are any, they must be very small.

A number of points were added to Weinland's description, and several errors corrected by Leuckart (1863, pp. 397-400) from a study of material obtained from Weinland.

That *Hymenolepis flavopunctata* Weinland from man is in reality the same form as *Tænia leptocephala* Creplin and *Tænia diminuta* Rudolphi was definitely established by Grassi (1888).

The most complete anatomical description of *Hymenolepis diminuta* which has appeared is that given by Zschokke (1889, pp. 63-73, figs. 21-24).

Two species very similar to *H. diminuta* are known, *Hymenolepis relicta* (Zschokke) from the rat, and *H. megaloon* Linstow from a gopher (*Spermophilus* sp.). The former, although described by Zschokke as a distinct species, is so nearly like *H. diminuta* that it is a question whether the two ought not to be united in the one species, *H. diminuta*. Practically the only distinguishing characteristics seem to be differences in the length and the number of segments, upon the basis of which it would be a very difficult matter to draw a line separating the two forms. The second form, *H. megaloon*, which was described briefly by Linstow (1901), resembles *H. diminuta* except in one or two minor details, and is a very nearly related species.

#### ANATOMICAL DESCRIPTION.

The following account of the anatomy of *Hymenolepis diminuta* is based upon previous descriptions supplemented by original observations upon specimens both from man and from rats:

#### EXTERNAL ANATOMY.

*Strobila*.—The length varies from 10 to 60 cm. and the breadth posteriorly is from 2.5 to 4 mm. or as much as (?) 7 mm. (Packard, 1900).

*Head*.—The size and form of the head (figs. 71-74) are variable, 200 to 600  $\mu$  in width, almost globular, but rather flattened; with 4 suckers, placed somewhat anteriorly, 80 to 160  $\mu$  in diameter, and a rudimentary, unarmed rostellum.

*Rostellum*.—The rostellum is in all essentials exactly similar to the rostellum of *Hymenolepis carioca* (see Ransom, 1902). When in a state of retraction the rostellum (figs. 72-74) has the appearance of a small elongated muscular sac embedded in the substance of the anterior part

of the head, with a very slender, tube-like cavity extending into its anterior end from the outside. This cavity is lined with cuticula continuous with the cuticula covering the head, and is thus evidently produced by a simple invagination. The rostellum is sometimes seen slightly protruded, forming thus a conical tip on the anterior surface of the head. When retracted, the rostellum measured in two specimens 100 by  $40\ \mu$  and 100 by  $80\ \mu$  in length and width, respectively. Linstow (1878b), as Grassi (18881) has remarked, erroneously described the rostellum of *H. diminuta* as a fifth sucker.

*Neck.*—The neck (fig. 72) is short, 0.5 mm. (Grassi, 18881), and is generally somewhat smaller in diameter than the head.

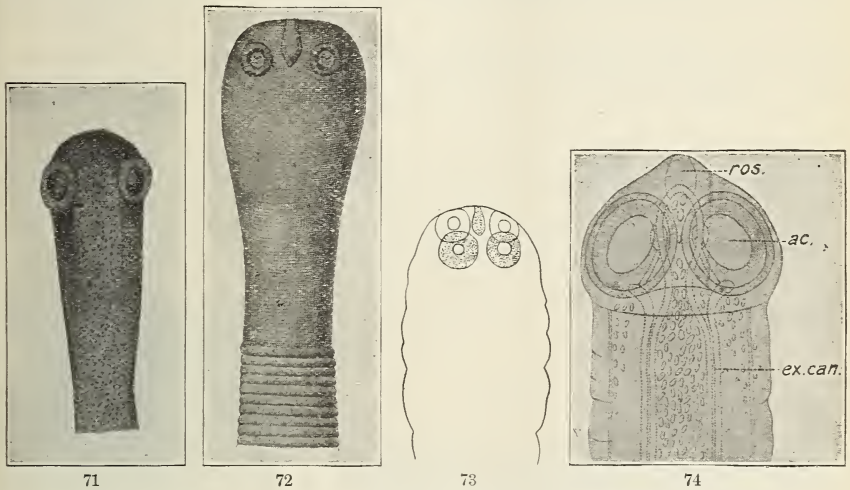


FIG. 71.—Head and neck of *H. diminuta* from man. Enlarged. (After E. Parona, 1884, fig. 4.)

FIG. 72.—Head and anterior portion of *H. diminuta* from rat. Enlarged. (After Zschokke, 1889, pl. 1, fig. 21.)

FIG. 73.—Head of *H. diminuta*. Enlarged. (After Grassi, 18881, pl. 11, fig. 5.)

FIG. 74.—Head of *H. diminuta*: *ac.*, sucker; *ex. can.*, excretory canals; *ros.*, rostellum. Enlarged. (After Grassi, 18881, pl. 11, fig. 2.)

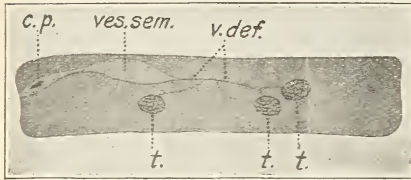
*Segments.*—The segments number 800 to 1,000 (Zschokke, 1889), 1,300 (Magalhães, 1896). As in nearly all tapeworms of numerous segments this character will be found to vary greatly. The young segments are 20 times as wide as long. The width of mature segments is 15 to 20 times the length, 6 to 10 times, or even not so much as twice, the length. The posterior borders of the segments are only slightly longer than the anterior borders of the following segments, and the appearance of serration is thus only slightly marked.

*Genital pores.*—The genital pores (figs. 75–77, 79, 80, 82, 83, 85, 87) are unilateral, situated on the left side in the anterior part of each segment at about the junction of the anterior and middle thirds. Occasionally the genital pore opens on the opposite side of the segment, but comparatively only a very few segments have the genital openings on the right side instead of the left.

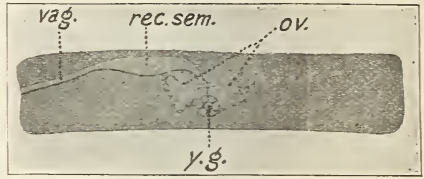


*Calcareous corpuscles* are present, more commonly noticed in the anterior part of the strobila, are of variable size and form, but generally oval, measuring 8 to 13  $\mu$  by 4 to 6  $\mu$  (fig. 74).

NERVOUS SYSTEM.—Two prominent *longitudinal nerve trunks* extend



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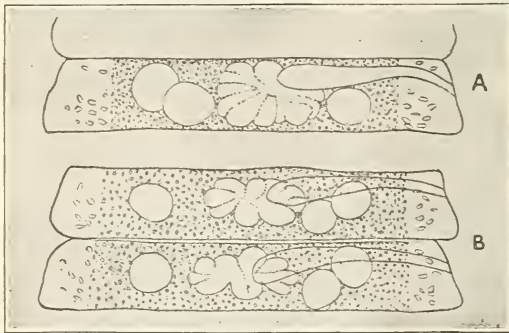


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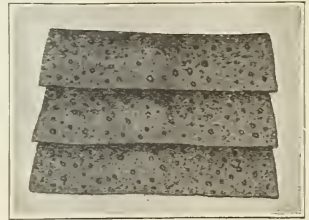
FIG. 75.—Proglottid of *H. diminuta* showing male organs: *c. p.*, cirrus pouch; *t.*, testis; *v. def.*, vas deferens; *ves. sem.*, vesicula seminalis. Enlarged. (After Grassi, 1888l, pl. 11, fig. 10.)

FIG. 76.—Proglottid of *H. diminuta* showing female organs: *ov.*, ovary; *rec. sem.*, receptaculum seminis; *vag.*, vagina; *y. g.*, yolk gland. Enlarged. (After Grassi, 1888l, pl. 11, fig. 10.)

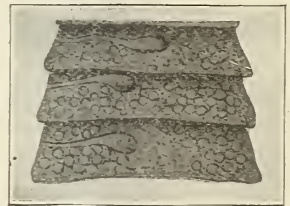
throughout the strobila, one on each side, situated a short distance laterad from the excretory vessels. Two small *accessory longitudinal nerves* are also present on each side, lying close to the dorsal and ventral sides, respectively, of the main lateral longitudinal nerve. In



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FIG. 77.—Proglottids of *H. diminuta* showing usual, A, and unusual, B, position of testes. Enlarged. (After Grassi, 1888l, pl. 11, fig. 14.)

FIG. 78.—Portion of strobila of *H. diminuta* about 4 cm. from the head. Enlarged. (After E. Parona, 1884, fig. 5.)

FIG. 79.—Portion from the middle of strobila of *H. diminuta*. Enlarged. (After E. Parona, 1884, fig. 6.)

each segment also, according to Zschokke (1889), the lateral trunks give off in the anterior and posterior regions of the proglottis, respectively, two nerves which run mediad, one in the cortical portion of the parenchyma, i. e., outside the layer of transverse muscle fibers,



and the other in the central portion, namely, beneath the transverse muscles. These undoubtedly represent commissures which are known to occur in other forms, connecting the lateral longitudinal nerves. In the regions where these commissural nerves are given off the lateral nerves present *ganglionic enlargements* (Zschokke, 1889). The

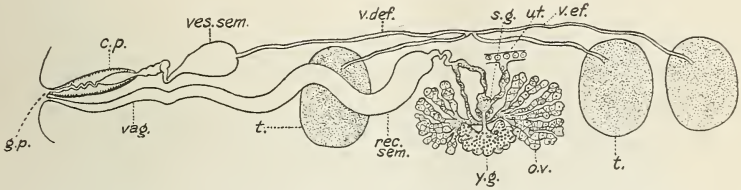


FIG. 80.—Male and female organs of *H. diminuta*. Transverse section: *c. p.*, cirrus pouch; *g. p.*, genital pore; *ov.*, ovary; *rec. sem.*, receptaculum seminis; *s. g.*, shell gland; *t.*, testis; *ut.*, uterus; *vag.*, vagina; *v. def.*, vas deferens; *v. ef.*, vas efferens; *ves. sem.*, vesicula seminalis; *y. g.*, yolk gland. Enlarged. (After Zschokke, 1889, pl. 2, fig. 22.)

nerve trunks turn inward in the scolex, become thicker and are united at the base of the rostellum by a commissure richly supplied with nerve cells. Four nerves extend forward along the sides of the rostellum, within which, also, nervous elements are distinguishable. Although neither an anterior nerve ring surrounding the anterior part of the rostellum, nor nerves to the suckers have been definitely seen, Zschokke (1889) considers their existence probable, upon the basis of analogy with other forms.

**MUSCULAR SYSTEM.**—Besides the subcuticular *circular* and *longitudinal muscle* fibres, there are present throughout the strobila, longitudinal, transverse, and dorso-ventral muscle fibers. The *longitudinal fibers* are arranged in bundles of 8 to 15 fibers which are placed in two series, an outer series or layer just beneath the layer of flask-like subcuticular cells which lie beneath the cuticula, and a second series, more or less distinct from the first, and more internally situated. The bundles are connected by numerous oblique fibers. The number of bundles is variable, but the bundles of the outer layer are more numerous than those of the second. Following the longitudinal fibers forward into the neck and scolex, the fibers of the outer series are seen, by the study of sections, to be derived from subcuticular longitudinal fibers of that region, while the fibers of the inner series continue on into the scolex and attach to the suckers and rostellum, relations already established by Lühe (1894,

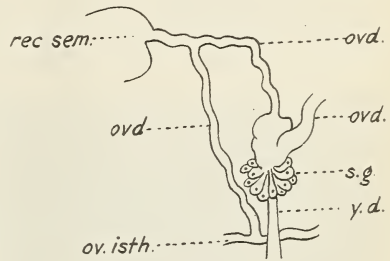


FIG. 81.—Point of union of female canals of *H. diminuta*: *ovd.*, oviduct; *ov. isth.*, isthmus connecting the right and left lobes of the ovary; *rec. sem.*, receptaculum seminis; *s. g.*, shell gland; *y. d.*, yolk duct. Enlarged. (After Zschokke, 1889, pl. 2, fig. 23.)

of the inner series continue on into the scolex and attach to the suckers and rostellum, relations already established by Lühe (1894,

1896) for other species, and referred to above in connection with *Hymenolepis nana*.

*Transverse fibers* are comparatively few, and are prominent at all, only in the region where one segment joins the next. The *dorso-ventral fibers* are also more prominently developed near the junction of the segments.

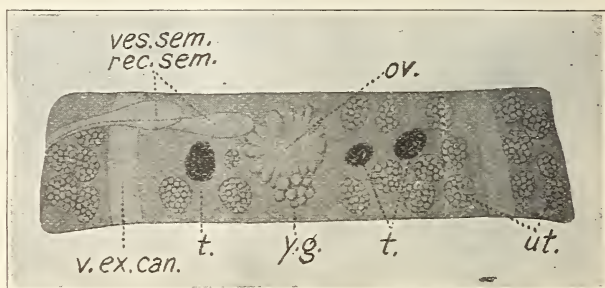


FIG. 82.—Proglottid of *H. diminuta* by transmitted light. Uterus developed and containing ova: *ov.*, ovary; *t.*, teste; *ut.*, uterus; *ves. sem.*, *rec. sem.*, vesicula seminalis and receptaculum seminis; *v. ex. can.*, ventral lateral excretory canal; *y. g.*, yolk gland. Enlarged. (After Grassi, 1888, pl. 11, fig. 12.)

The rostellum is supplied with longitudinal and circular fibers, an outer longitudinal and inner circular (Zschokke, 1889). In the scolex there are found muscle fibers running in various directions, with various attachments.

**EXCRETORY SYSTEM.**—The excretory canals (figs. 74, 82, 84, 88) are laterally situated. The ventral pair as usual are much the larger, and are connected in the posterior part of each segment by a transverse canal (fig. 84) of smaller caliber. The dorsal canals lie close to the dorsal side of the ventral canals, and are much smaller except in the scolex and the anterior part of the strobila where the ventral canals are of small diameter, only a little larger than the dorsal canals (fig. 74). In the scolex there is an anastomosis of the

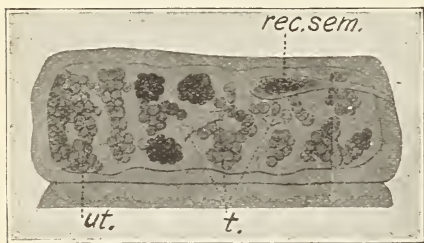


FIG. 83.—Proglottid of *H. diminuta* further developed than fig. 79: *rec. sem.*, receptaculum seminis; *t.*, remnants of testes; *ut.*, uterus. Enlarged. (After Grassi, 1888, pl. 11, fig. 12.)

four canals behind the rostellum. Extending forward from this anastomosis, there are two loops, one on either side of the rostellum, into which also, the excretory system is extended by means of four very slender canals, which unite in the rostellum to form two closed loops, the dorsal canal of each side uniting with the corresponding ventral canal. Similar loops, as found by Mingazzini (1899), in *Hymenolepis nana* have already been mentioned in connection with that form.

**REPRODUCTIVE SYSTEM.**—The male reproductive organs develop more rapidly than the female and reach maturity sooner.

The cirrus pouch and vagina cross the excretory canals and the longitudinal nerve on the dorsal side.

*Male organs.*—Three *testes* (*t.*, figs. 75, 80, 82, 83) are normally present, two to the right and one to the left of the mass of female glands which occupy the median portion of the proglottis. Two testes, however, may often be found occupying the side toward the genital pore and only one on the other side (fig. 77B). Exceptionally, also, only two may be present, or there may be four to six. In shape the testes are oval or spherical and when fully developed occupy nearly the entire thickness of the central parenchyma.

*Vasa efferentia* (*v. ef.*, fig. 80) lead from the dorsal sides of the testes, and the three canals converging to meet near the median line in the dorsal portion of the central parenchyma unite to form the *vas deferens* (*v. def.*, figs. 75, 80) which passes laterad near the anterior border

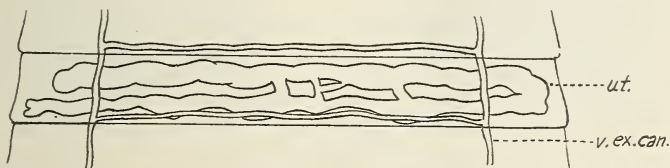


FIG. 84.—Longitudinal section of proglottid of *H. diminuta* showing the arrangement of the uterus; *ut.*, uterus; *v. ex. can.*, ventral lateral excretory canal. Enlarged. (After Zschokke, 1889, pl. 2, fig. 24.)

of the segment, in the direction of the genital pore. Before reaching the cirrus pouch, however, the vas deferens is dilated to form a large pyriform *seminal vesicle* (*ves. sem.*, figs. 75, 80, 82).

The *cirrus pouch* (*c. p.*, figs. 75, 80) is claviform and well supplied with circular and longitudinal muscle fibers. Fibers directed in an oblique or spiral direction are also often apparent. The vas deferens within the cirrus pouch is supplied with muscle fibers: it becomes narrow and forms the slender *cirrus*, an organ bent and twisted when in a state of retraction, but which may be straightened and extended through the genital pore a distance of 50 to 60  $\mu$ . In sections the cirrus is occasionally seen protracted and entered for a considerable distance into the vagina of the same segment.

After they have fulfilled their function, the testes degenerate, but traces of them are often distinguishable even in the oldest segments (*t.*, fig. 83). After it once reaches maturity the cirrus pouch continues with little apparent change to the end of the strobila.

*Female organs.*—The *vagina* (*vag.*, figs. 76, 80) opens into the genital pore on the ventral side of the cirrus pouch. It soon dilates into a large, elongated, and very prominent *seminal receptacle* (*rec. sem.*,

figs. 76, 80-83) which extends inward nearly to the middle line. It is this organ filled with sperm which appears as the yellow spot, and furnished the name *flavopunctata* of Weinland. Weinland erroneously interpreted this organ as a testis.



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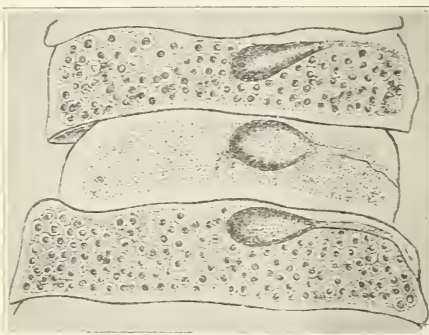


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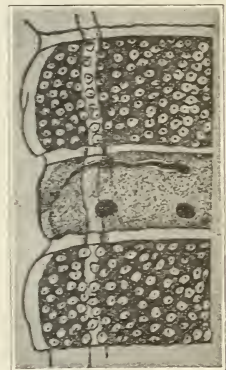
FIG. 85.—Immature proglottids of *H. diminuta*. Enlarged. (After Stein, 1882, pl. 13, fig. 10.)

FIG. 86.—Gravid proglottids of *H. diminuta*. Enlarged. (After Stein, 1882, pl. 13, fig. 11.)

Near the middle of the segment the seminal receptacle ends and opens into the middle of the *oviduct* by a narrow tube (fig. 81).



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FIG. 87.—Gravid proglottids of *H. diminuta* (one sterile). Enlarged. (After Leuckart, 1863, p. 399, fig. 117.)

FIG. 88.—One-half of two fertile joints of *H. diminuta*, with that of an intervening sterile joint. Enlarged. (After Leidy, 1884a, p. 111.)

The *ovary* (*ov.*, figs. 76, 80, 82) is more or less bilobed and situated in the median part of the proglottis. The *oviduct* (*ovd.*, figs. 80, 81) leading from the ovary runs first forward, is joined by the narrow



tube from the seminal receptacle, then turns toward the ventral surface and backward, and in the midst of the complex of cells, known as the shell gland, is joined by the duct from the yolk gland. The *shell gland* (*s. g.*, figs. 80, 81) is a little rounded mass which lies between the right and left lobes of the ovary. The *yolk gland* (*y. g.*, figs. 76, 80-82) is lenticular in shape and situated on the ventral side of the shell gland and somewhat more posteriorly. With respect to the main body of the ovary the yolk and shell glands are posterior (caudad).

From its point of union in the shell gland with the yolk duct the oviduct turns forward and empties into the *uterus* on the dorsal side of the anterior part of the ovary (figs. 80, 81). The uterus at first is simply a transversely elongated mass of cells without a cavity, but as it develops becomes hollowed out and

the tube thus formed grows in various directions, sending out diverticula and increasing in size generally so as to gradually fill up practically the entire proglottis. After the uterus begins to grow actively the ovary quickly disappears. The yolk gland, however, remains apparent for a long time. According to the degree of development which the uterus has reached it is evident that the appearances will be somewhat different. Zschokke (1889), for example, has described a

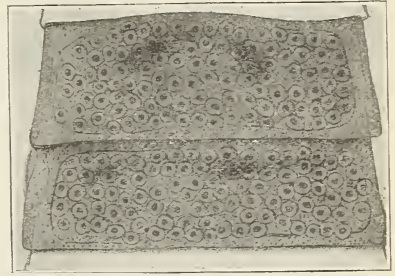


FIG. 89.—Proglottids of *H. diminuta* from posterior portion of strobila. Enlarged. (After E. Parona, 1884, fig. 7.)

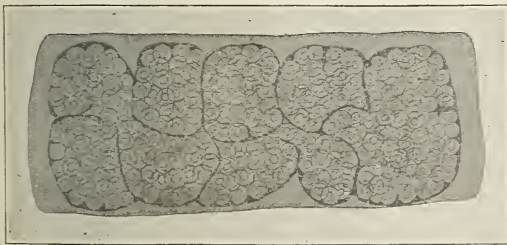


FIG. 90.—Proglottis of *H. diminuta* containing fully developed ova, rendered transparent with potash. Enlarged. (After Grassi, 18881, pl. 11, fig. 15.)

condition (fig. 84) in which the uterus has the form of two transverse canals uniting at one side so as to form a loop, the two limbs of which are also connected at various other points. Grassi (18881) noticed in sections of segments in which the uterus had not reached its final development, that it appeared as a large number of cavities of various sizes communicating with one another (figs. 82, 83).

As the uterus grows the diverticula become crowded together, and the eggs form a more or less compact mass occupying nearly the whole segment. The adult uterus, at first sight apparently a simple sac filled with eggs, is thus seen to be more complex; its cavity, although continuous, is broken up by incomplete partitions, and by innumerable pro-

glottis. After the uterus begins to grow actively the ovary quickly disappears. The yolk gland, however, remains apparent for a long time. According to the degree of development which the uterus has reached it is evident that the appearances will be somewhat different. Zschokke (1889), for example, has described a condition (fig. 84) in which the uterus has the form of two transverse canals uniting at one side so as to form a loop, the two limbs of which are also connected at various other points. Grassi (18881) noticed in sections of segments in which the uterus had not reached its final development, that it appeared as a large number of cavities of various sizes communicating with one another (figs. 82, 83).

cesses invaginated from its walls, penetrating everywhere among the eggs as in *Hymenolepis nana*, but in this case more pronounced, so that

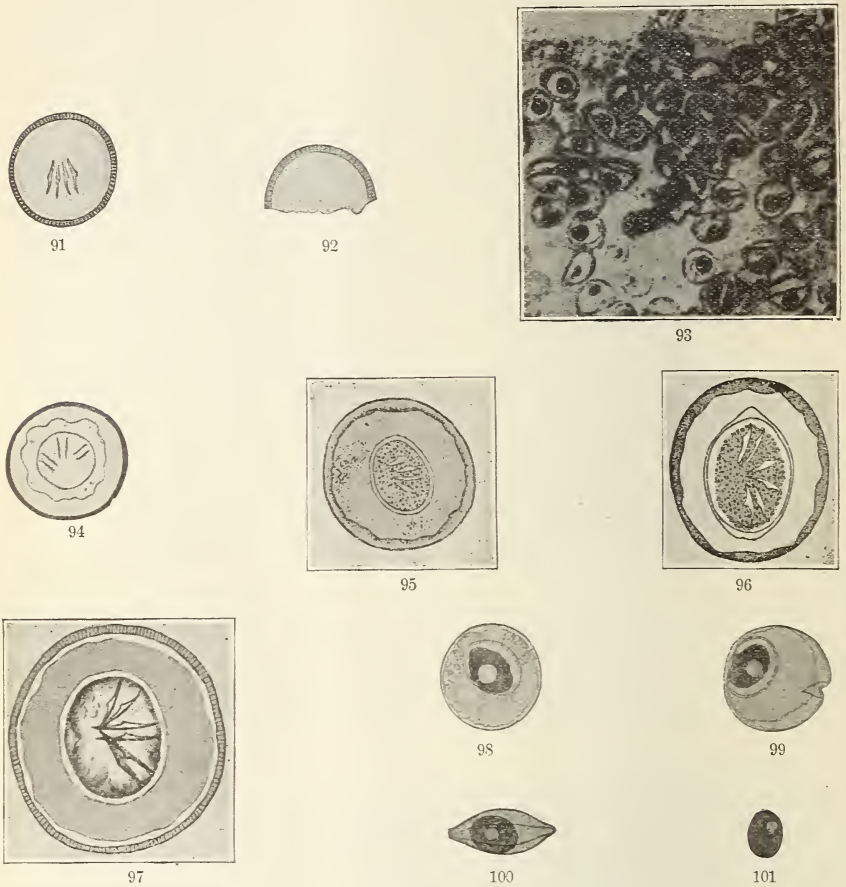


FIG. 91.—Egg of *H. diminuta* from the woodmouse (*Mus sylvaticus*). Median focus. Enlarged. (After Dujardin, 1845a, pl. 12, fig. G1.)

FIG. 92.—Egg of *H. diminuta* from the woodmouse (*Mus sylvaticus*). Superficial focus. Enlarged. (After Dujardin, 1845a, pl. 12, fig. G2.)

FIG. 93.—Eggs of *H. diminuta* from man. Enlarged. (After Stein, 1882, pl. 13, fig. 12.)

FIG. 94.—Egg of *H. diminuta* from rat. Enlarged. (After Zschokke, 1889, pl. 2, fig. 30.)

FIG. 95.—Egg of *H. diminuta* from man, as seen in feces. Enlarged. (After Grassi, 1888, pl. 11, fig. 16.)

FIG. 96.—Egg of *H. diminuta* from man, as seen in feces. Enlarged. (After Grassi, 1888, pl. 11, fig. 19.)

FIG. 97.—Egg of *H. diminuta* from man. (E. Parona's (1884) case.) Enlarged. (After Bizzozero, 1889a, pl. 4, fig. g'').)

FIG. 98.—Egg of *H. diminuta* from man. Enlarged. (After Weinland, 1861, pl. 4, fig. 12.)

FIG. 99.—Fully developed egg of *H. diminuta* from man, with outer membrane broken and intermediate substance protruding. Enlarged. (After Weinland, 1861, pl. 4, fig. 13.)

FIG. 100.—Egg of *H. diminuta* in glycerin; outer membrane folded. Enlarged. (After Weinland, 1861, pl. 4, fig. 14.)

FIG. 101.—Embryo of *H. diminuta* surrounded by inner membrane. Outer membrane and intermediate substance have been torn away. Enlarged. (After Weinland, 1861, pl. 4, fig. 15.)

the result may be compared to a sponge, the meshes of which are filled by the eggs (figs. 87–90).

In *Hymenolepis diminuta* from man it is a very common thing to find numerous sterile proglottids (figs. 87, 88). In these segments the female organs fail to develop properly, and no embryos are produced. Such segments are readily apparent in the older portions of the strobila, by reason of their clear color, due to the absence of eggs, which give fertile segments a somewhat dark or brownish color. These sterile segments have been noticed by nearly everyone who has ever observed *H. diminuta* from man, while in specimens from the rat they are much less common. Leidy (1884a), for example, gives the following succession of fertile and sterile segments in a fragment about 8 cm. long. The fertile segments are indicated by roman type, the sterile by italics:

2, 1, 2, 1, 6. 1. 1, 1, 5. 1. 18, 1, 3, 1, 3, 5. 1. 1, 3, 4, 1, 1. 3. 1. 1. 5. 2, 7, 1, 10, 1, 6, 3, 3, 15, 1. 2. 2. 2. 2.

*Eggs.*—The eggs as first seen in the uterus do not differ apparently from the eggs as found in the ovary. The shell is not formed by the immediate action of the so-called shell gland, as might be supposed, during the passage of the egg through the part of the oviduct surrounded by this gland, but only becomes apparent during the progress of the development of the embryos in the uterus. When fully formed the embryo possesses a shell in which 3 layers may be distinguished, an *outer*, a *middle*, and an *inner* (figs. 91–101). Both the embryo and its shell increase in size after development is begun, until the final stage of the eggs as they are thrown off in the feces is reached. The egg as seen in the feces or in the oldest segments is spherical (figs. 91–95, 97). The *outer membrane* is comparatively thick and delicately striated radially, and is more or less yellowish in color. The *inner membrane* closely invests the embryo or onchosphere and is somewhat oval in shape, often with two polar papillæ (fig. 96), as in *Hymenolepis nana*, but so far as is known without filaments. This membrane is thinner than the outer. Between the outer and inner membranes is an intermediate layer of granular structure, apparently albuminous in character.

When the outer envelope is broken away (fig. 99), this intermediate layer remains and is seen to have a smooth external contour, as though limited by a very thin but distinct membrane. In sections of preserved material this granular intermediate layer is commonly found drawn away from both the outer and inner envelopes, and bounded internally and externally by a very delicate smooth membrane of chitinous appearance. In the granular mass are three or four or more prominent deeply staining nuclei. It is to the activity of these nuclei, or of the oëlls to which they belong, that the formation and growth of the shell of the embryo seem to be due.

It is only in eggs of the oldest segments that the radial structure of the outer membrane can be distinguished; in eggs of younger seg-



ments this striation is not apparent, and the membrane is much thinner. In still younger segments the eggs are considerably smaller and the shape is commonly oval.

A number of authors give the sizes of the eggs as follows:

Dujardin (1845a, p. 579): Outer envelope, 62 to 74  $\mu$ ; inner envelope, 41 to 42  $\mu$ ; embryo, 32 to 36  $\mu$ ; hooks, 15 to 17  $\mu$ .

Weinland (1858, p. 55): Outer envelope, 54  $\mu$ ; embryo, 24  $\mu$ .

Leuckart (1886a, pp. 661-663, from Weinland's material): Outer envelope, 60  $\mu$ ; embryo, 30  $\mu$ ; hooks, 17  $\mu$ .

E. Parona (1884): Outer envelope, 58 to 68  $\mu$ .

Grassi (1888l): Outer envelope, 70 to 86  $\mu$ ; embryo, 36 by 28  $\mu$ ; hooks, 11  $\mu$ .

Zschokke (1889), no measurements given.

Leidy (1884a, p. 110): Outer envelope, 72  $\mu$ ; a few oval eggs 80 by 72  $\mu$ ; embryos, 40 by 32  $\mu$ .

Magalhães (1896): Outer envelope, about 59.5  $\mu$ ; embryo, about 34  $\mu$ .

Sonsino (Sonsino & Zschokke, 1896): Outer envelope, 75  $\mu$  and 80 by 75  $\mu$ ; hooks, 14  $\mu$ .

In measurements which I have made of eggs of specimens, both from the rat and from man (Leidy's material), the outer envelope ranged, in both cases, from 64 to 80  $\mu$ ; the inner, 24 by 20  $\mu$  to 36 by 28  $\mu$ ; the hooks, 14 to 16  $\mu$ .

The middle pair of hooks differed from the other two pairs in the same manner as mentioned above in connection with *H. nana*, namely, they were more delicate and the ventral root was only very slightly developed.

Besides the eggs of ordinary size it is not uncommon to find in mature segments now and then an egg considerably smaller, round or slightly oval, with the outer envelope much thicker than is usual in the larger eggs. Four such specimens gave sizes ranging from 40 by 40  $\mu$  to 40 by 48  $\mu$ .

Sonsino (Sonsino & Zschokke, 1896, p. 939) has found that the ova will remain alive in water at least fifteen days.

#### DEVELOPMENT AND LIFE HISTORY.

It is to the observations of Grassi & Rovelli (1888b, 1889a, 1889b, 1892a) that we owe our knowledge of the life history of *Hymenolepis diminuta*. Their results (as given in Grassi & Rovelli, 1892a, pp. 31-33, 90-92) are as follows:

All attempts at direct infestation resulted negatively.

The cysticercoïds were first found in the larva of the meal moth and its adult (*Asopia farinalis*), then in young and adult earwigs (*Anisobis annulipes* Lucas), and finally in adults of beetles (*Aeïs spinosa* (Linnæus) and *Scaurus striatus* (Fabricius)). They live in the abdom-



inal cavity of these various insects amid the adipose tissue, sometimes in very considerable numbers.

The larva of *Asopia farinalis* is very common in dwelling houses all over Europe, where it feeds upon organic materials, refuse, flour, meal, etc. In the moth stage it is frequent in April and October. This moth is also common in America, and, in fact, is almost cosmopolitan in its distribution.

On account of its wide geographical range corresponding with the distribution of *H. diminuta*, Grassi considers that *Asopia* is probably the normal intermediate host of the tapeworm in question. It is said by Grassi that rats prey actively not only upon the larval, but also upon the adult moths.

*Acis spinosa* lives in the south of Europe, *Scaurus striatus* in the south of France, in Italy, Spain, and Greece; both belong to the same family of beetles (Tenebrionidæ), related to that in which *Tenebrio* belongs, the latter, the supposed intermediate host of *Tænia microstoma*.

Twenty or more cysticercoids from *Anisolabis* were administered to white rats, which were entirely free from tapeworms; after 3 days the head of *H. diminuta* with a very short neck was observed in the intestine; after a week the neck had become longer,  $\frac{1}{2}$  cm., with

no trace of segments; in 15 days the worm had become quite long but without yet having reached maturity. The experiments were repeated for all the other intermediate hosts; the results were constantly positive, and the adult worms obtained corresponded perfectly to *H. diminuta*.

Two experiments were tried on man, one upon Sig. Calandrucchio, which resulted negatively, and one upon a second individual (adult male); in the second case, 15 days after the ingestion of the cysticercoids (from *Acis spinosa*), the ova of *H. diminuta* appeared in the feces, and after treatment with male fern, numerous specimens of the tapeworm were passed.

The *cysticercoïd* was observed only in the mature stage, free or provided with an adventitious connective tissue capsule, evidently derived from the host. Its size is measured by a few tenths of a milli-

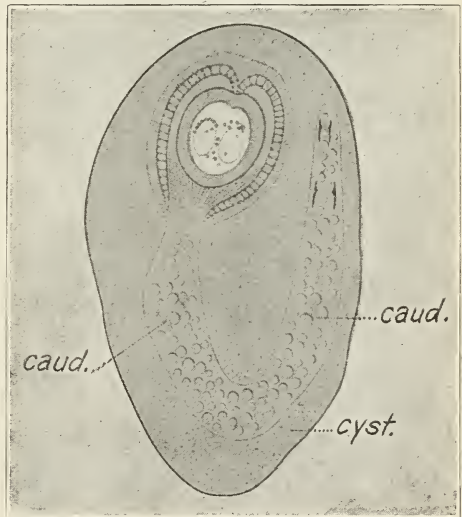


FIG. 102.—Encysted cercocystis of *H. diminuta*: caud., caudal appendage; cyst., adventitious capsule inclosing the cercocystis. Enlarged. (After Grassi & Rovelli, 1892a, pl. 4, fig. 1.)

meter. Like the cysticercoïd of *Hymenolepis nana*, it has a body and a tail, and may therefore be termed a cercocystis. The tail is rather long, two or three times the length of the body (fig. 102). As in the case also of *H. nana* (see p. 40) the body is a gastrula-like structure, with an anterior opening and a secondary cavity formed by invagination.

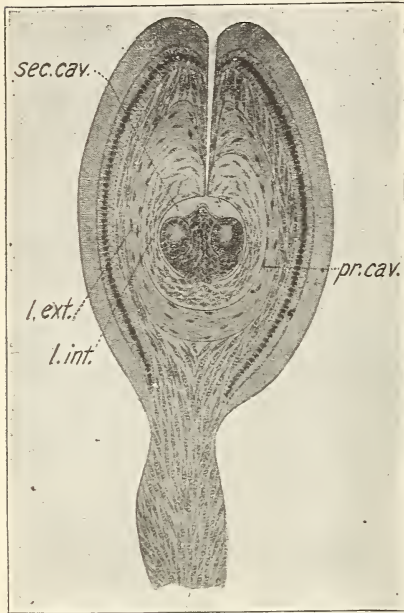


FIG. 103.—Longitudinal section of cercocystis of *H. diminuta*: *l. ext.*, external wall; *l. int.*, internal wall; *pr. cav.*, primary cavity; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 4, fig. 3.)

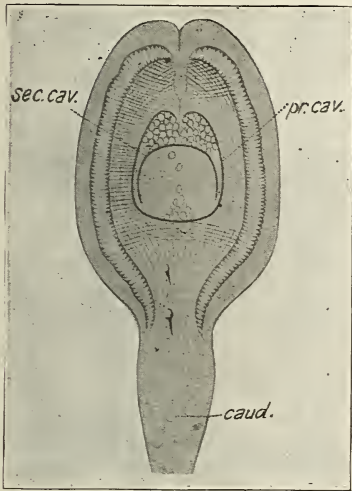
with these two bands of cells, cut across, corresponding to the poles of the ellipse (fig. 104). The inner wall is composed of a layer of reticular connective tissue, rich in cells and calcareous corpuscles, and lined with cuticula. The relations of the scolex are the same as in the cercocystis of *H. nana* (see p. 40); that is, it lies within the second cavity, and is attached behind to the inner wall by a peduncle, which in this case, however, is thicker and shorter than in *H. nana*. The primitive cavity is well defined in good preparations; it does not extend into the tail. The anterior opening of the secondary cavity is very narrow and deep. The four excretory vessels form horseshoe-like loops in the scolex in relation with the inner wall (fig. 106).



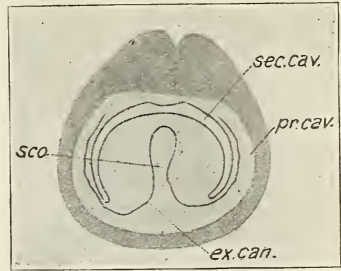
FIG. 104.—Cross section of cercocystis of *H. diminuta*: *l. ext.*, external wall; *l. int.*, internal wall; *pr. cav.*, primary cavity; *sco.*, scolex; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 4, fig. 2.)

The embryonal hooks are frequently evident, commonly four upon the tail and two upon the most posterior part of the body proper (fig. 105).

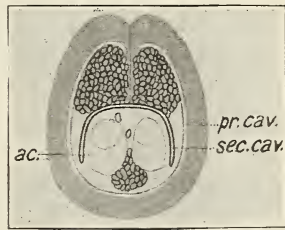
Since the tail was sometimes found branched and at other times (in *Anisolabis*) the cysticercoids were united by their tails into groups of 3 or 4, and since occasionally in *Acis spinosa* a smaller cysticercoid would be found attached by the tip of the tail to the thickest part of the tail of a cysticercoid of ordinary size, it seemed probable to Grassi that in certain cases the cysticercoid of *H. diminuta* is capable of proliferation.



105.



106.



107.

FIG. 105.—View of cercocystis of *H. diminuta*, showing muscle fibres: *caud.*, caudal appendage; *pr. cav.*, primary cavity; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 4, fig. 4.)

FIG. 106.—Longitudinal section through the body of a cercocystis of *H. diminuta*: *ex. can.*, excretory canal; *pr. cav.*, primary cavity; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 4, fig. 6.)

FIG. 107.—Longitudinal section through the body of a cercocystis of *H. diminuta*: *ac.*, sucker; *pr. cav.*, primary cavity; *sec. cav.*, secondary cavity. Enlarged. (After Grassi & Rovelli, 1892a, pl. 4, fig. 5.)

Cysticercoids, single or proliferated, were often found dead, having undergone a degeneration by which they became brown, and the details of structure indistinct. In some cases, in *Acis spinosa*, the adventitious capsule was present and very thick; live cysticercoids were found encapsulated in *Anisolabis*.

In a footnote (Grassi & Rovelli, 1892a, p. 33) it is stated that more recently a stage in the development of the cysticercoid was found which showed that in *H. diminuta* the formation of the rostellum and suckers precedes the invagination as in *Hymenolepis nana*.



ABSTRACTS OF CASES OF HYMENOLEPIS DIMINUTA  
IN MAN.

AMERICA.

Boston, 1842..... 1 case.

WEINLAND (1858) was the first to record the occurrence of this tapeworm in man. His account (1858, p. 59) in part reads as follows:

"Among the helminthological specimens with which Dr. J. B. S. Jackson kindly furnished us for further investigation, from the collection of the Medical Improvement Society, Boston, there was a phial containing a number of pieces of a small tapeworm. In the catalogue of the collection we find these specimens mentioned under No. 903, with the following words: 'A (second) specimen of *Bothriocephalus*, 3 feet in length, and from  $\frac{1}{2}$  line to  $1\frac{1}{4}$  lines in width; from an infant. The joints are very regular, except at one extremity, where they approach the triangular form, are very delicate, and but slightly connected, as shown in a drawing by Doctor Wyman. From a very healthy infant 19 months old; it had been weaned about six months, and had had the usual diet from that time. The worm was discharged without medicine, its presence having never been suspected. 1842. Dr. Ezra Palmer, jr.'"

Weinland recognized the fact that this specimen was not a *Bothriocephalus*, but a tapeworm belonging to a group of Tæniids, whose members thus far had only been found in small omnivorous or insectivorous mammalia (mice, shrew-mice, etc.) and birds." Not perceiving its identity with *Tænia diminuta*, he accordingly described it as a new species, at the same time establishing it as the representative of a new genus, and gave it the name of *Hymenolepis flavopunctata* (see p. 82).

Philadelphia, Pa., 1884..... 1 case.

LEIDY (1884a, p. 110, 1884b, p. 137) recorded a case of *Tænia flavopunctata* (= *Hymenolepis diminuta*) from a 3-year-old child, who had expelled several pieces of at least 3 worms after treatment with santonin. This child, native of Philadelphia but of German parentage, had been weaned at 20 months, and since then partaken of the same food as its parents. The specimens from this case are preserved in the Helminthological Collection (No. 841) of the Bureau of Animal Industry.

São Paulo, Brazil, 1893..... 1 case.

LUTZ (1894, p. 62) received a tapeworm for determination which had been passed after treatment with santonin, by a 2-year-old child, daughter of Portuguese settlers, living at São Paulo, Brazil. The specimen had about 960 segments, several of which were sterile: the posterior segments were completely filled with eggs, and the rostellum was rudimentary and unarmed. Lutz identified it as *Hymenolepis diminuta*, and by comparison with specimens from the rat confirmed Grassi's observations as to the identity of *Tænia flavopunctata* of man and *Tænia diminuta* of the rat. The parasite is very common among the rats of São Paulo.

Rio Janiero, Brazil, 1896..... 1 case.

The patient in this case (MAGALHÃES, 1896) was a mulatto child, 20 months old, born in a neighboring city, but for about a year living in Rio Janiero, at the zoological gardens, where her father was employed. The child had been suffering for about 3 months with diarrhea, frequently sanguineous in character. Treatment by various physicians was of no avail. According to the parents, the child's food consisted exclusively of milk and beef tea. After the administration of a dose of calomel a worm was passed, which was referred by the attending physician to Magalhães for determination, who identified it as *Hymenolepis diminuta*. The child's parents asserted that a similar worm, somewhat longer, and also fragments, had been passed previously. The child continued to suffer with diarrhea. Treatment



with male fern was tried; no worms were expelled, and the diarrhea still persisted, ceasing at times, but always recurring. Later an *Ascaris* was passed, without improvement of the diarrhea.

**Philadelphia, Pa., 1900** ..... 1 case.

PACKARD (1900, p. 1551) describes the case of a woman, 40 years of age, native of Syria, who entered the Pennsylvania Hospital at Philadelphia, suffering with a hydatid cyst of the liver, from which she died. Shortly after admission she passed a fragment of a tapeworm 16.5 cm. long. The segments were 3 mm. wide by 1 mm. long. At the autopsy, about one month after the patient entered the hospital, a second specimen was found, attached to the intestine about 2.5 cm. above the ileocecal valve. The parasite was living when found and measured 27 cm. in length. The head was distinctly blackish in color, with a slight purple tinge, and measured 1 mm. long by 0.5 mm. wide. The neck was 1 cm. long and 1.5 mm. wide. "In most of the segments there is seen at one edge a little elevation extending in from the edge about 1 mm., corresponding apparently to what has been spoken of in some specimens as the yellow spot. These little elevations do not form a complete series, as occasionally there is found a segment where the elevation is on the opposite side of the segment. There is no appearance about the worm of a true yellow spot. On dehydrating segments in absolute alcohol and clearing in oil of cloves there is seen in each of a series of 7 segments a dark line less than  $\frac{1}{10}$  of a millimeter in thickness extending inward toward the center of the segment to a length of 3 mm." There was no branching uterus, the entire proglottis being transformed into an egg-sac. The brownish line extended inward from the left side in 5 segments, from the right side in 2, as follows: 1, r, l, r, l, l, l. Viewed under a high power, the brownish line was seen to be a canal, sometimes appearing to terminate in a bulbous enlargement.

#### EUROPE.

**Alfort, France, before 1810** ..... 1 case.

RAILLIET (1892c) makes mention of two fragments of a tapeworm, measuring together 18 to 20 cm. in length, and a number of fragments belonging to a second example. These specimens, which were labeled as coming from man, belong to an old helminthological collection established by Chabert, second director (1780-1810) of the museum at Alfort. Rudolphi visited this collection about the year 1804, and since he has made no mention of such specimens in any of his works on helminthology, Railliet has come to the conclusion that they probably date from a time between 1804 and 1810. These specimens were determined by both Railliet and Zschokke as *Hymenolepis diminuta*.

**Varese, Italy, 1884** ..... 1 case.

A 2-year-old girl living in the neighborhood of Varese had declined in health and lost her usual good spirits. Pieces of tapeworm having been recognized in her stools, she was brought to the hospital of Varese for treatment. E. PARONA (1884), who examined the case, found no abnormalities of importance in the physical examination. The feces contained the eggs of *Ascaris* and cestode eggs resembling those of *Tenia solium* but much larger. Castor oil and ethereal extract of male fern were administered and 4 complete worms, 12 to 20 cm. long, each provided with a head, were passed. Treatment was repeated, but no more worms, with the exception of an *Ascaris*, were expelled. Parona considered these worms probable examples of *Hymenolepis flavopunctata* Weinland, a determination which Grassi (18881) confirmed after examining some of the material.

**Catania, Sicily, 1887-1888** ..... 2 cases.

GRASSI (18881, p. 498, GRASSI & ROVELLI, 1888b) records a case of *Hymenolepis diminuta* from a 12-year-old girl, who exhibited no symptoms of importance. After

anthelmintic treatment, she passed, besides a *Tænia solium*, 2 specimens of *Hymenolepis diminuta*, measuring 25 and 30 cm., one of which possessed a head.

In the second case (GRASSI, 18881, p. 500, GRASSI & ROVELLI, 1888b) infection was induced experimentally by feeding a man with cysticercoïds (see p. 95).

**Pisa, Italy, 1895** ..... 1 case.

A specimen of tapeworm, which had been passed by a boy in September, 1895, after the administration of an anthelmintic, was referred to Sonsino (SONSINO & ZSCHOKKE, 1896) for determination by Doctor Modigliano, of the Pisa hospital. Sonsino determined the specimen as *Tænia flavopunctata* Weinland (= *H. diminuta*). Zschokke made a similar determination. The description of the worm and the figure of an egg given by Sonsino leave no doubt as to its identity.

**Centuripe, Sicily, 1900** ..... 2 cases.

PREVITERA (1900) discovered in the feces of sulphur miners in Sicily the eggs of a tapeworm, undoubtedly of the species *Hymenolepis diminuta*.

The first case was that of a sulphur miner, male, 11 years old. There was an average of one egg in every preparation. The eggs were mostly spherical, almost double the size of eggs of *Tænia solium*; two membranes were present, separated by an abundant hyaline substance which shriveled in glycerine and drew away from the outer membrane; the latter was distinctly striated radially; some of the eggs were uncolored, some yellowish. Male fern was administered. Whether any worms were passed is not known, but a reëxamination of the feces some days later showed no eggs present.

In the feces from the other case 2 to 3 eggs were found in every preparation. The subject of this case was not seen, nor was any information regarding his age, physical condition, etc., obtainable.

## ANALYSIS OF CASES.

### AGE AND SEX OF INDIVIDUALS AFFECTED.

Of the 12 cases reported, 5 were females, 3 were males, while the sex of the remaining 4 cases is not given. Two were adults, one of whom was a woman, 40 years of age; 8 were children, and the ages of 2 were not given. Four were between 1½ and 2 years: 1 was 3 years, and 2 were 11 and 12 years, respectively; the age of the other child was not given.

### SITUATION OF THE PARASITE IN THE INTESTINE.

In the single autopsy which has been performed (Packard, 1900) the worm was found attached 2.5 cm. above the ileo-cecal valve.

### NUMBER OF SPECIMENS PRESENT.

The number of specimens present in infected individuals has varied from 1 to 4. In 4 cases there was 1; in 3 cases, 2; in 1 case, 3; and in 1 case, 4.

### OTHER PARASITES PRESENT.

In 2 cases the presence of *Ascaris* and in 1 case the presence of *Tænia solium* was noted; 1 case was suffering with a hydatid cyst of the liver.

## SYMPTOMATOLOGY.

Symptoms were absent in practically all the cases; in one case there was said to be a decline in health and in another there was a diarrhea of three months' standing, which, however, was not cured by the expulsion of the parasite.

## DIAGNOSIS.

The diagnosis rests upon the discovery of fragments of the worm or its eggs in the feces.

## TREATMENT.

Almost any vermifuge seems to be sufficient to expel the parasite. A simple cathartic has caused its expulsion, and in one case the worm was passed without medicine.

## PROPHYLAXIS.

Prophylaxis against *H. diminuta* consists in avoiding the ingestion of any of the various insects which may act as intermediate hosts, (1) by following the general rule of cleanliness with regard to what is placed in the mouth, (2) by keeping food protected from insects, especially the larvæ of *Asopia farinalis*, and (3) the destruction of rats and mice, and of the insects concerned, especially the meal moth, which in its larval stages is common about dwellings.

The Lanceolate Tapeworm—HYMENOLEPIS LANCEOLATA (Bloch, 1782)  
Weinland, 1858.

## HISTORICAL REVIEW.

This tapeworm has long been known as a parasite of geese and ducks, but only recently has it been found in man. An epidemic of intestinal helminthiasis among geese in 1710 in Germany reported by Frisch (1727b) has been attributed to this form. Bloch (1779a), according to Rudolphi (1810, p. 84), refers to the worm under the name *Tænia anseris*. Pallas (1781) associated the worm under consideration with others from rabbits and fishes, and placed them in a single species, which he called *Tænia acutissima*. In 1782 Bloch published the first distinctive description and figures (figs. 108, 109) of the worm, calling it *Tænia lanceolata*. Goeze (1782a) shortly afterwards described and figured it (fig. 110) under the same name. Since then it has been commonly found in the European countries by various authors, but apparently has never been recorded for America. Only one case of *Hymenolepis lanceolata* in man has been reported, and that case was in Europe (Zschokke, 1902a, b). It is, therefore, a rare parasite of man, and is not very likely to be encountered in this country.

## ANATOMICAL DESCRIPTION.

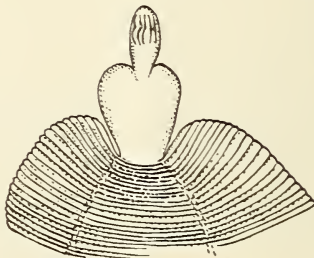
The external characteristics of *Hymenolepis lanceolata* are so well marked that its recognition has never been considered difficult. Feuer-



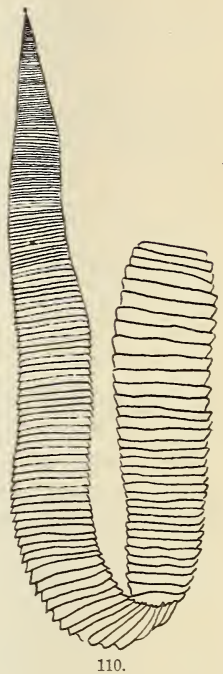
108.



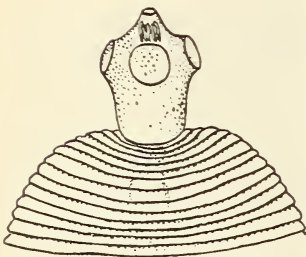
109.



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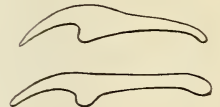
111.



112.



113.



114.

Fig. 108.—Head and strobila of *H. lanceolata*. Natural size. Original type figure. (After Bloch, 1782a, pl. 1, fig. 5.)

Fig. 109.—Head and anterior portion of *H. lanceolata*. Enlarged. Original type figure. (After Bloch, 1782a, pl. 1, fig. 6.)

Fig. 110.—Head and strobila of *H. lanceolata* from a goose. Natural size. (After Goeze, 1782a, pl. 29, fig. 3.)

Fig. 111.—Head with protracted rostellum and anterior portion of *H. lanceolata*. Enlarged. (After Mégnin, 1881, pl. 4, fig. 3.)

Fig. 112.—Head with retracted rostellum and anterior portion of *H. lanceolata*. Enlarged. (After Railliet, 1886, p. 267, fig. 163A, also Railliet, 1893, p. 300, fig. 195A.)

Fig. 113.—The eight hooks upon the rostellum of *H. lanceolata*. Enlarged. (After Krabbe, 1869, pl. 6, fig. 143.)

Fig. 114.—Two isolated hooks of *H. lanceolata*. Enlarged. (After Krabbe, 1869, pl. 6, fig. 144.)

eisen (1868a) was the first to study its internal anatomy; his incomplete and in some respects incorrect description has recently been revised and added to by Wolffhügel (1900b) and Cohn (1901b).



The length has been given as 30 to 130 mm.; the width posteriorly may attain a maximum of 18 mm., more commonly 7 to 12 mm. The *strobila* gradually increases in width from before backward, reaching its greatest width a short distance anterior of the posterior extremity, then becomes narrower again and rounded off posteriorly, thus giving the worm its characteristic lancet shape (figs. 108, 110). In the anterior portion of the *strobila* the segments are 30 to 35 times as broad as long; in segments with mature reproductive organs the ratio between length and breadth is 1 to 40; in the last segments, 1 to 25. The *head* (figs. 111, 112), which is very small in comparison to the rest of the worm, possesses a retractile *rostellum* armed with a single crown of hooks, usually 8 in number (fig. 113). The *hooks* (fig. 114) have a long dorsal root, a short ventral root, and a prong equal in length to about two-thirds of the dorsal root. They measure 31 to 35  $\mu$  (Krabbe, 1869). The short *neck*, together with the head, is often retracted into the anterior part of the *strobila*. The *segments*, about 300 in number, in specimens 85 or 90 mm. in length (Zschokke, 1902a, b), are very much broader than long throughout the *strobila*. The *genital pores* open on the right-hand margin of the *strobila*, near the anterior border of each segment.<sup>a</sup>

## INTERNAL ANATOMY.

The internal anatomy of the head has not been studied.

*Calcareous bodies* are numerous, especially in the cortical parenchyma.

**NERVOUS SYSTEM.**—The lateral *longitudinal nerves* are situated laterad of the longitudinal excretory vessels; each main lateral nerve is accompanied by two accessory nerves—one dorsal and one ventral (fig. 117).

**MUSCULAR SYSTEM.**—The usual subcuticular muscle fibers are present, an *outer circular* and an *inner longitudinal layer*. *Dorso-ventral muscle fibers* likewise are present, and are very powerfully developed.

The well-developed *longitudinal muscle system* (*l. m.*, fig. 121) is arranged mostly in two layers, with about 90 to 100 (Wolffhügel, 1900b) or 200 (Zschokke, 1902a, b) bundles in each layer. In the cortical parenchyma, i. e., between the outer muscle layer and the cuticula, there are numerous scattering longitudinal muscle fibers. Lying inside the inner layer in both the dorsal and the ventral halves of the *strobila* there are two bundles of muscle fibers, one on each side of the median line, separated by a space equal to about one-sixth the

<sup>a</sup>Dujardin (1845a, p. 562) describes the pores of *Tenia lanceolata* as irregularly alternate, mentioning also the presence of 10 hooks on the rostellum; two circumstances which indicate the probability that he had under observation another species.

breadth of the strobila (Wolffhügel, 1900b). Wolffhügel found that the two longitudinal muscle layers become more or less fused in the older segments so that they can no longer be distinguished as separate. Cohn (1901b, p. 320) asserts that the layers in question can not be considered individually distinct at all, as they nowhere preserve their identity for any considerable distance. He also differs with Wolffhügel in that he failed to find the four isolated bundles described by the latter author. Zschokke (1902a, b) has noticed numerous diagonal fibers connecting here and there the bundles of longitudinal fibers.

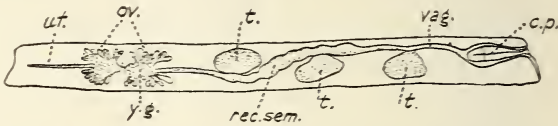


Fig. 115.—Isolated proglottid of *H. lanccolata*: *c. p.*, cirrus pouch; *ov.*, ovary; *rec. sem.*, receptaculum seminis; *t.*, testis; *ut.*, probably the primordium of the uterus; *vag.*, vagina. Enlarged. (After Feuersen. 1868a, pl. 10, fig. 17.)

EXCRETORY SYSTEM.—There are two pairs of lateral longitudinal excretory vessels, of which the ventral pair are the larger (fig. 117). According to Wolffhügel (1900b) transverse canals connecting the longitudinal vessels are lacking, but Cohn (1901b) has found a system of small anastomosing canals extending across the posterior portion of each segment, connecting the longitudinal canals and taking the place of the transverse canals. The excretory vessels and the lateral longitudinal nerves pass on the ventral side of the cirrus pouch.

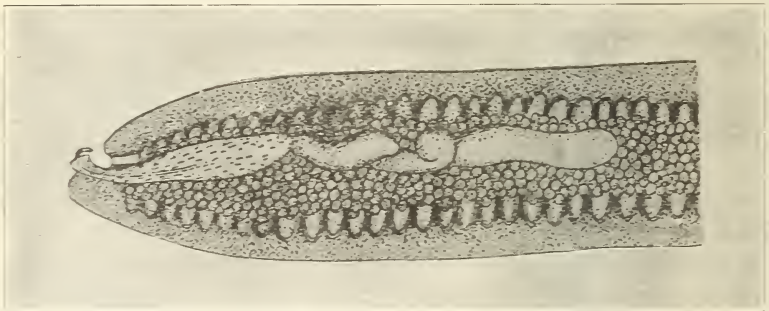


Fig. 116.—Transverse section of proglottid of *H. lanccolata*. Enlarged. (After Mégnin, 1881, pl. 4, fig. 6.)

REPRODUCTIVE SYSTEM.—The reproductive organs lie in the central portion of the parenchyma, i. e., inside of the longitudinal muscle layer, and are so distributed that the female glands occupy the sinistral third of the proglottis; the three testes and a portion of the seminal receptacle the middle third; and the remainder of the seminal receptacle, the vagina (*sensu stricto*), the seminal vesicle and the cirrus pouch, the dextral third (figs. 115, 117).

*Male organs.*—The three *testes* (*t.*, figs. 115, 117) are oval, with

their long axes directed parallel to the transverse axis of the segment, and occupy almost the entire thickness of the inner parenchyma. The two dextral testes are in the posterior half, the other one in the anterior half of the proglottis.

The *vas deferens* (*v. def.*, fig. 117) in its course to the genital pore lies toward the dorsal side of the segment; after passing the right hand testis it swells out into a large *seminal vesicle* (*ves. sem. ex.*, fig. 117) then somewhat reduced again in size describes one or two S-shaped loops, and enters the base of the *cirrus pouch*.

The latter (*c. p.*, figs. 115, 117) is a powerfully developed club-shaped organ, which when straight lies entirely in the anterior half of the proglottis; it may be bent S-like and lie in the posterior half of the proglottis as well. It measures in length from 0.82 to 1.2 mm. and from 60 to 190 $\mu$  in width at different points. Externally the cirrus pouch (fig. 121) is supplied with a layer of longitudinal muscle lamellae (*m. pl.*) which has a maximal thickness of 50 $\mu$ . The lamellae become gradually thinner toward the distal end of the cirrus pouch, and in its outer third are reduced to a very thin muscle layer. In relation to the muscle lamellae is a thick layer of myoblastic cells (*my.*). Within the cirrus pouch the *vas deferens* is again enlarged to form a *seminal vesicle* which lies toward the dorsal side. The *vas deferens*, near the junction of the middle and outer thirds of the cirrus pouch, becomes reduced in size, turns mediad and, running along the ventral wall of the pouch again swells out into a small spindle-shaped vesicle in

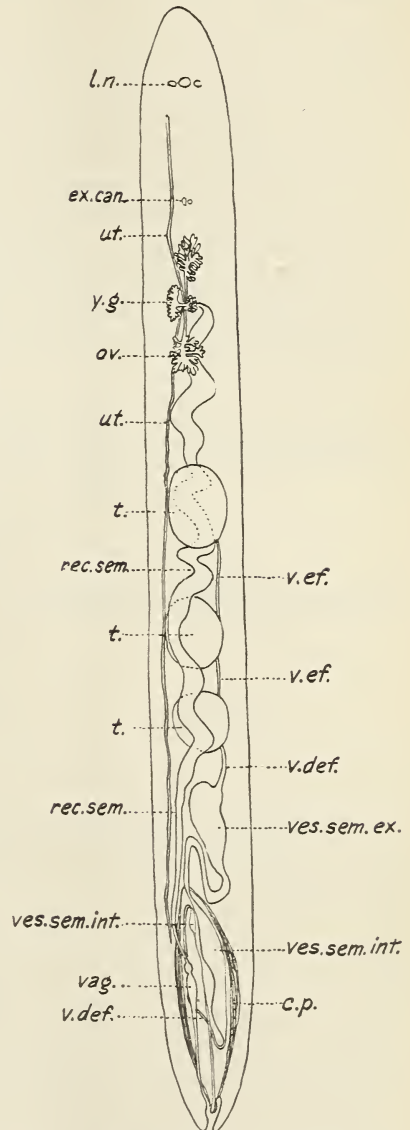


Fig. 117.—Transverse section of proglottis of *H. lanceolata*: *c. p.*, cirrus pouch; *ex. can.*, excretory canals; *l. n.*, lateral longitudinal nerves; *ov.*, ovary; *rec. sem.*, receptaculum seminis; *t.*, testis; *ut.*, uterus; *vag.*, vagina; *v. def.*, vas deferens; *v. ef.*, vas efferens; *ves. sem. ex.*, vesicula seminalis externa; *ves. sem. int.*, vesicula seminalis interna; *y. g.*, yolk gland. Enlarged. (After Wolffhügel, 1900b, p. 51, fig. 2.)



the proximal portion of the latter. The vas deferens now runs laterad again and near the junction of the inner and middle thirds of the pouch is transformed into the *cirrus* which opens outwardly at the tip of the cirrus pouch through the common genital pore. The portion of the vas deferens within the cirrus pouch, including the cirrus, is supplied with longitudinal and circular muscle fibers of varying degrees of development in different portions. The cirrus (figs. 117, 121) is armed with spines and is often seen evaginated through the genital pore. The distal end of the cirrus pouch may also be extruded for some distance through the pore (fig. 120). The occurrence of a loop in the vas deferens, in its course within the cirrus pouch, as described for *Hymenolepis lanceolata*, has been demonstrated, also, in a number of other tapeworms, in *Hymenolepis fasciata*

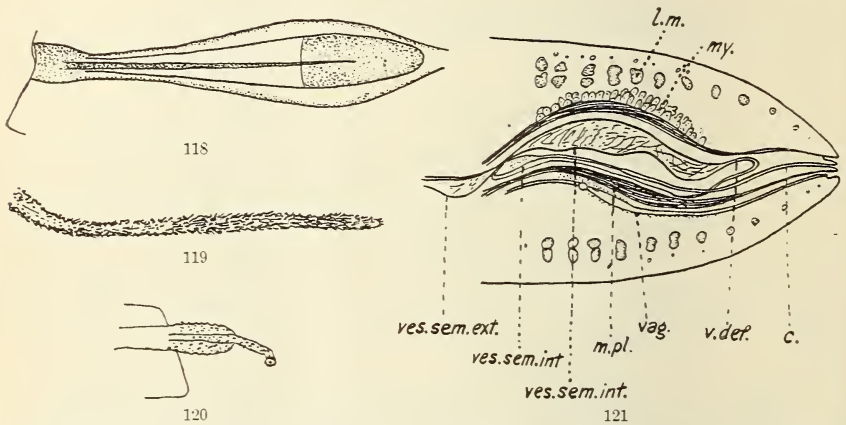


FIG. 118.—Cirrus pouch and cirrus of *H. lanceolata*. Enlarged. (After Feueisen, 1868a, pl. 10, fig. 9.)

FIG. 119.—Isolated cirrus of *H. lanceolata*. Enlarged. (After Mègnin, 1881, pl. 4, fig. 7.)

FIG. 120.—Extruded cirrus and tip of cirrus pouch of *H. lanceolata*. Enlarged. (After Feueisen, 1868a, pl. 4, fig. 8.)

FIG. 121.—Transverse section of proglottid of *H. lanceolata*, showing the cirrus pouch and vagina: *c.*, cirrus; *l. m.*, longitudinal muscles; *m. pl.*, muscle plates of cirrus pouch; *my.*, myoblasts; *vag.*, vagina; *v. def.*, vas deferens; *ves. sem. ext.*, vesicula seminalis externa; *ves. sem. int.*, vesicula seminalis interna. Enlarged. (After Wolffhügel, 1900b, p. 52, fig. 3.)

(Krabbe) by Feueisen (1868a), in *Hymenolepis gracilis* by Wolffhügel (1900a), in *Hymenolepis megalops* by Ransom (1902), and apparently in *Hymenolepis sinuosa* by Kowalewski (1895).

*Female organs.*—The *vagina* (*vag.*, figs. 115, 117, 121) begins at the genital pore as a tube about  $7\mu$  in diameter, lying ventral and somewhat anterior with respect to the middle line of the cirrus pouch, and courses along the ventral side of the latter. The outer two-thirds of the portion in relation with the cirrus pouch (fig. 122), according to Wolffhügel, is lined by thick cuticula covered with fine spines, and is supplied with an inner layer of circular muscle fibers and an outer layer of longitudinal fibers. During its course inward from the genital pore the vagina increases gradually in diameter (to about  $20\mu$ ).



then becomes abruptly narrower, losing an outer layer of cells and its lining of thick cuticula; at the point of constriction the vagina is surrounded by a spherical bulb consisting of short thick muscle fibers, longitudinally directed with respect to the vagina (figs. 122, 123). Beyond the muscle bulb the vagina is prolonged as a thin walled tube, and sooner or later widens out into an elongated *seminal receptacle*, about  $85\mu$  in diameter. The receptacle (*rec. sem.*, figs. 115, 117) extends mediad on the anterior side of the two dextral testes, and on the posterior side of the sinistral testis, and continues past the median line into the sinistral third of the proglottis to empty into the oviduct.

The *ovary* (*ov.*, figs. 115, 117) consists of two lobes connected by a slender isthmus. The *oviduct* takes its origin from the middle of the isthmus (fig. 124); about midway between its origin and the point at which it is surrounded by the *shell gland*, it is joined by the seminal

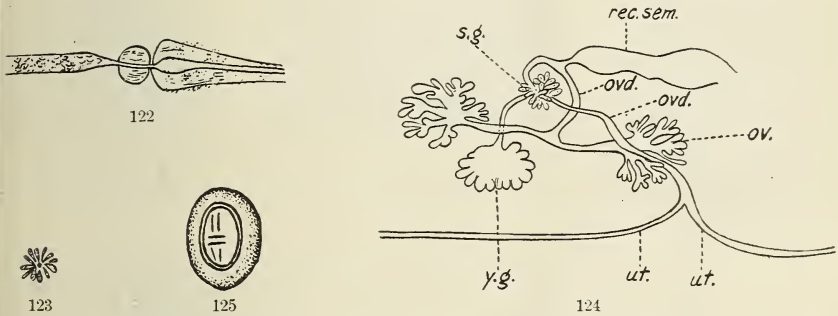


FIG. 122.—Portion of the vagina of *H. lanceolata*. Longitudinal section. Enlarged. (After Wolffhügel, 1900b, p. 53, fig. 4.)

FIG. 123.—Transverse section of vagina of *H. lanceolata* through muscle bulb. Enlarged. (After Wolffhügel, 1900b, p. 53, fig. 5.)

FIG. 124.—Diagrammatic representation of the female canals of *H. lanceolata*: *ov.*, ovary; *ovd.*, oviduct; *rec. sem.*, receptaculum seminis; *s. g.*, shell gland; *ut.*, uterus; *y. g.*, yoke gland. Enlarged. (After Wolffhügel, 1900b, p. 54, fig. 6.)

FIG. 125.—Egg of *H. lanceolata*. Enlarged. (After Railliet, 1886, p. 267, fig. 163B; also Railliet, 1893, p. 300, fig. 195B.)

receptacle. The *yolk gland* (*y. g.*, figs. 117, 124) is ventrally situated with respect to the ovary and has a diameter equal to about one-third the length of the proglottis. The *yolk duct* (fig. 124) joins the oviduct in the *shell gland* (*s. g.*, fig. 124), a rounded body about  $100\mu$  in diameter located dorsal of the isthmus of the ovary. From the shell gland the oviduct continues forward and ventrad to the *uterus* (*ut.*, figs. 117, 124). The latter at first is a thin canal, ventrally situated near the anterior boundary of the proglottis, extending transversely beyond the excretory canals on either side. In gravid segments the uterus becomes a large sac with outpocketings which push between the longitudinal muscle bundles and out against the cuticula, thus filling most of the segment.

*Eggs.*—The egg (fig. 125) is spherical or oval and possesses an outer and an inner membrane. The latter closely invests the embryo and is

widely separated from the outer membrane. There is thus considerable similarity between the eggs of *Hymenolepis lanceolata* and *H. diminuta*. The *outer membrane* of the former, however, does not become thickened as in the case of the latter, but remains very thin, and the intervening substance between the two membranes is less conspicuous and does not ordinarily present the appearance of a third membrane as is usual in the latter instance. The *inner membrane* occasionally presents polar papillæ as in *H. diminuta* and *H. nana*. The egg measures, according to Railliet (1893), 50 by 35  $\mu$ , and the embryonal hooks, according to Krabbe (1869), 8  $\mu$ . According to my own measurements the outer membrane varies from 60 to 100  $\mu$  in diameter, the inner measures 30 by 25  $\mu$  to 40 by 25  $\mu$ , and the hooks from 12 to 15  $\mu$ .

#### DEVELOPMENT AND LIFE HISTORY.

Mrázek (1896, p. 11) mentions some cysticercoïds which he found in various small crustaceans of the family Cyclopidae. These cysticercoïds agreed as to the form and size of the hooks with *H. lanceolata*, and Mrázek accordingly considered them the intermediate stage of the tapeworm under discussion. He gives no description or figures, merely remarking that the cysticercoïds are almost exactly similar to those of *Tænia setigera*.

Dadai (1900a) found a large number of specimens of a cercocystis (figs. 126-130) in small crustacea, *Diaptomus spinosus* Dadai, collected from stagnant pools in Vadkert, Hungary, which he would identify with *Hymenolepis (Drepanidotænia) lanceolata* (Bloch).

The cyst is more or less spherical with a remarkably thick wall, the circular and longitudinal muscle layers being remarkably well developed. A few calcareous corpuscles were seen in the inner layer of the parenchyma of the cyst wall. The cyst measured 0.23 to 0.28 mm. in length, and 0.18 to 0.23 mm. in diameter.

The head was occasionally seen extruded through the anterior opening of the cyst (fig. 128), but usually was found retracted and filling the cavity of the cyst almost entirely (figs. 126, 127). The rostellum was either retracted into the scolex or protruded. The number (8) and the form of the hooks (fig. 127) was the same as in *H. lanceolata*, but their size was very different, 55 to 60  $\mu$ , while in the latter they measure only 31 to 35  $\mu$ , which renders the correctness of Dadai's identification rather doubtful.

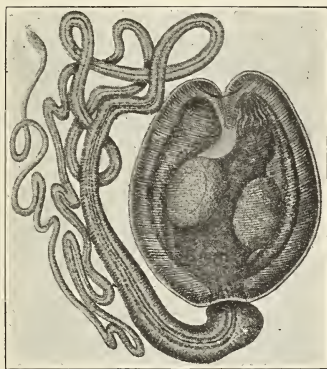
The caudal appendage is remarkable for its very great length. Its surface is very frequently marked by ring-like corrugations. It consists chiefly of granulated protoplasm and sometimes of masses of parenchyma cells: running lengthwise through its center is a characteristic thread-like structure, which consists of a dark, finely granular layer of protoplasm surrounding a still darker central fiber (fig. 127).

It has not been proved experimentally that the larvæ found by Mrázek or Dadai represent the intermediate stage of *Hymenolepis lanceolata*; but, upon the assumption that they or similar larvæ belong to the life-cycle, it may be presumed that infection occurs as follows:

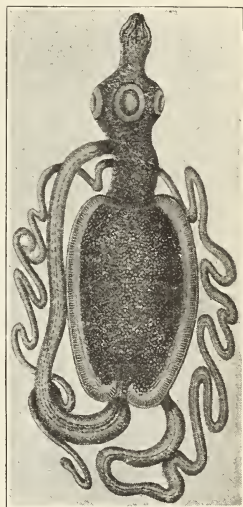
The embryos of the tapeworm are distributed in stagnant pools by



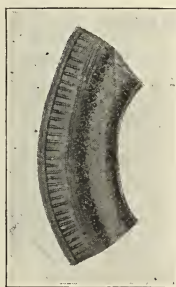
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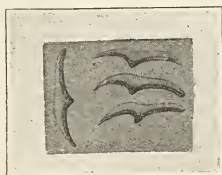
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129



130

Fig. 126.—Cercocystis of [?] *H. lanceolata* with scolex retracted. Enlarged. (After Dadai, 1900a, pl. 10, fig. 9.)

Fig. 127.—Cercocystis of [?] *H. lanceolata* with scolex retracted. Enlarged. (After Dadai, 1900a, pl. 10, fig. 7.)

Fig. 128.—Cercocystis of [?] *H. lanceolata* with scolex protruded. Enlarged. (After Dadai, 1900a, pl. 10, fig. 11.)

Fig. 129.—Section of wall of cercocystis of [?] *H. lanceolata*. Enlarged. (After Dadai, 1900a, pl. 10, fig. 12.)

Fig. 130.—Hooks of cercocystis of [?] *H. lanceolata*. Enlarged. (After Dadai, 1900a, pl. 10, fig. 8.)

infected ducks or geese, and are ingested, whether before or after hatching is not known, by *Cyclops*, *Diaptomus*, or other small crustacea, in the body cavity of which the intermediate stage develops. The intermediate stage is introduced into the alimentary canal of some animal, normally a duck or a goose, by the drinking of water contain-

ing infected crustacea, and the definitive stage may then be developed. Although certainly very unusual, it appears that development of the adult following the ingestion of the intermediate stage may occur also in the human intestine.

### ABSTRACT OF CASE OF HYMENOLEPIS LANCEOLATA IN MAN.

Breslau, Germany, 1902 ..... 1 case.

This unique case has been reported by ZSCHÖKKE (1902a, b), who received two tapeworms for determination which had been passed spontaneously, at two different times, by a 12-year-old boy at Breslau. The heads were lacking in both specimens, but a careful anatomical study left no doubt as to their identity with *Hymenolepis lanceolata* (Bloch).

### COMPENDIUM OF THE THREE PARASITES, H. NANA, H. DIMINUTA, AND H. LANCEOLATA, ARRANGED ACCORDING TO THEIR HOSTS.

In the following compendium all the hosts reported for any of the three tapeworms discussed in this paper are included.

(\*) Signifies that I have examined specimens of the parasite from the host in question.

(?) Signifies that the correctness of the determination is considered doubtful.

#### Class MAMMALIA—Mammals.

##### Order PRIMATES.

###### HOMO SAPIENS—Man.

* <i>Hymenolepis nana</i> .....	Intestine.
<i>Hymenolepis nana</i> .....	? Bladder (p. 56).
* <i>Hymenolepis diminuta</i> .....	Intestine.
<i>Hymenolepis lanceolata</i> .....	Intestine.

##### Order RODENTIA—Rodents.

###### MUS DECUMANUS<sup>a</sup>—Brown or Norway rat.

* <i>Hymenolepis nana</i> .....	Intestine.
* <i>Hymenolepis diminuta</i> .....	Intestine.

###### MUS RATTUS ALEXANDRINUS—Egyptian or roof rat.

<i>Hymenolepis diminuta</i> .....	Intestine.
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###### MUS RATTUS—Black rat.

<i>Hymenolepis nana</i> .....	Intestine.
<i>Hymenolepis diminuta</i> .....	Intestine.

<sup>a</sup>The names used for the rodents in this list are those given by Trouessart, 1889-1898, *Catalogus mammalium tam viventium quam fossilium. Nova editio (prima completa)*. 8°. Berlin.



**MUS MUSCULUS**—House mouse.

<i>Hymenolepis nana</i> .....	Intestine.
<i>Hymenolepis diminuta</i> .....	Intestine.

**MUS MINUTUS**—Dwarf field mouse.

<i>Hymenolepis nana</i> .....	Intestine.
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**MUS SYLVATICUS**—Wood, or field mouse.

<i>Hymenolepis nana</i> .....	Intestine.
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**ELIOMYS QUERCINUS**—Garden dormouse.

<i>Hymenolepis nana</i> .....	Intestine.
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**RHIPIDOMYS PYRRHORHINUS.**

<i>Hymenolepis diminuta</i> .....	Intestine.
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**Class AVES**—Birds.**ANAS BOSCHAS DOMESTICA**—Tame duck.

<i>Hymenolepis lanceolata</i> .....	Intestine.
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**ANAS OBSCURA**—Black duck.

<i>Hymenolepis lanceolata</i> .....	Intestine.
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**ANSER ANSER DOMESTICUS**—Tame goose.

* <i>Hymenolepis lanceolata</i> .....	Intestine.
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**CAIRINA MOSCHATA**—Muscovy duck.

<i>Hymenolepis lanceolata</i> .....	Intestine.
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**ERISMATURA LEUCOCEPHALA**—White-headed duck.

<i>Hymenolepis lanceolata</i> .....	Intestine.
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**AYTHYA FERINA**—Pochard.

<i>Hymenolepis lanceolata</i> .....	Intestine.
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**AYTHYA NYROCA**—African teal.

<i>Hymenolepis lanceolata</i> .....	Intestine.
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**AYTHYA RUFINA**—Red-crested pochard.

<i>Hymenolepis lanceolata</i> .....	Intestine.
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**PHENICOPTERUS ROSEUS**—Flamingo.

<i>Hymenolepis lanceolata</i> .....	Intestine.
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**Branch ARTHROPODA**—Arthropods.**Class INSECTA**—Insects.**ASOPIA FARINALIS**—Meal moth.

<i>Hymenolepis diminuta</i> (larval stage) .....	Abdominal cavity.
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## ANISOLABIS ANNULIPES—Earwig.

*Hymenolepis diminuta* (larval stage) ..... Abdominal cavity.

## ACIS SPINOSA—Beetle.

*Hymenolepis diminuta* (larval stage) ..... Abdominal cavity.

## SCAURUS STRIATUS—Beetle.

*Hymenolepis diminuta* (larval stage) ..... Abdominal cavity.

**Class CRUSTACEA—Crustaceans.**

## Order COPEPODA.

## Family CYCLOPIDÆ.

Genera? species?

?*Hymenolepis lanceolata* (larval stage).

## DIAPTOMUS SPINOSUS.

?*Hymenolepis lanceolata* (larval stage).

## BIBLIOGRAPHY.

The following bibliography, compiled with the assistance of Mr. E. C. Stevenson, comprises the articles in which reference is made to one or more of the three species, *Hymenolepis nana*, *H. diminuta*, and *H. lanceolata*, and also, in a few instances only, articles which, while not bearing directly upon any of the three forms in question, have been referred to incidentally in the course of the present paper.

(\*) Indicates that the article so marked contains original observations concerning one or another of the above-named tapeworms.

The forms and abbreviations used are those employed in the Index-Catalogue of Medical and Veterinary Zoology, Bull. No. 39, Bureau of Animal Industry, United States Department of Agriculture, Washington [W<sup>a</sup>., Library of the Department of Agriculture; W<sup>c</sup>., Library of Congress; W<sup>m</sup>., Library of the Surgeon-General's Office of the United States Army; W<sup>s</sup>., Library of the Smithsonian Institution; Lib. Stiles, Library of Ch. Wardell Stiles, United States Public Health and Marine Hospital Service, Washington, D. C.].

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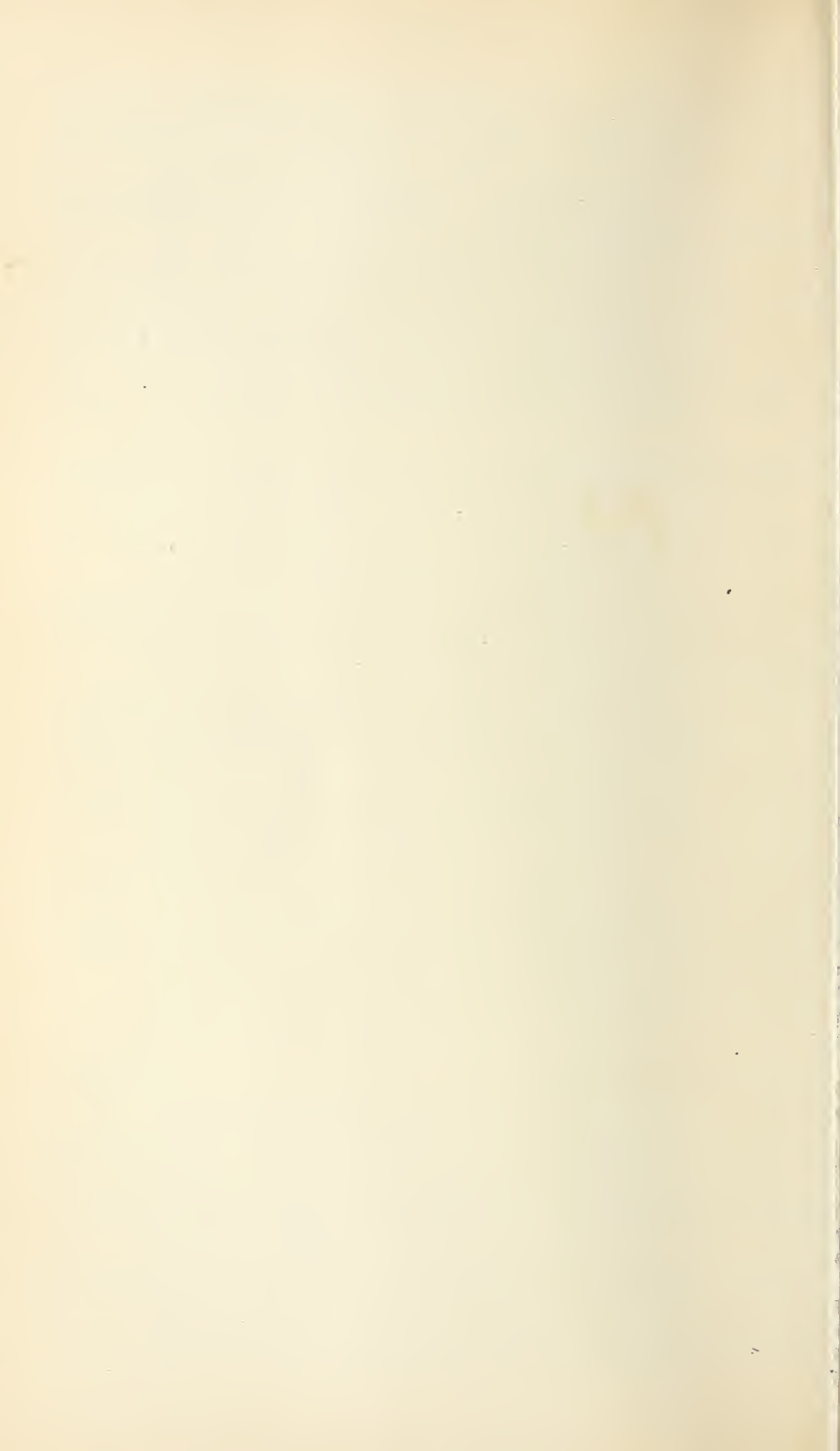
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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 19.

October, 1904.

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A METHOD FOR INOCULATING ANIMALS  
WITH PRECISE AMOUNTS.

BY

M. J. ROSENAU,  
DIRECTOR OF THE HYGIENIC LABORATORY.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.  
1904.

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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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1904.

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WALTER WYMAN, *Surgeon-General*.  
*United States Public Health and Marine-Hospital Service.*

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### DIVISION OF PHARMACOLOGY.

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# A METHOD FOR INOCULATING ANIMALS WITH PRECISE AMOUNTS.

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By M. J. ROSENAT, Director Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service.

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The need has long been felt in special lines of research work for a good method of inoculating animals with precise amounts. In the ordinary laboratory work great exactness in this regard is not an important matter, but in standardizing diphtheria antitoxins, and in the physiological tests of some drugs, and in certain lines of physiological chemistry, the greatest precision is essential.

With the ordinary methods in use in most laboratories, there is an unavoidable loss, resulting in an error of from 1 to 8 per centum. The usual method consists of first measuring the dilution, or the substance, into a graduate or other suitable vessel, and then drawing it up into the syringe, from which it is inoculated into the animal.

There are two principal sources of error in this practice, (1) the loss in the glass and (2) the loss in the syringe.

*The loss in the glass.*—If the fluid is drawn up into the syringe from a glass container a certain amount remains behind. In a series of 18 careful weighings this loss was found to average about one-half of 1 per cent, using 4 c.c. of fluid.

The loss from this source was determined by weighing a chemically clean conical graduate, then adding 4 c.c. of distilled water, taking care not to wet more surface than necessary, and again weighing to determine the amount of water. As much of the water as possible is drawn up into the syringe, tilting the graduate so as to get the last drop that drains to the bottom. The graduate is again quickly weighed before evaporation takes place to any appreciable extent. The difference between the weight of the wet glass and the dry glass of course gives the loss in the glass. The average loss in 4 c.c. was found to be 0.0192; that is, nearly two one-hundredths of a cubic centimeter, or about one-half of 1 per cent (0.48 per cent) of the amount of water used. Of course when less than 4 c.c. of fluid is used the percentage of loss increases in proportion.

The variation in the loss is shown in the following figures:

Loss in graduate, using 4 c. c. of water.	
( 1)	0. 0366
( 2)	. 0032
( 3)	. 0095
( 4)	. 0098
( 5)	. 0175
( 6)	. 0176
( 7)	. 0112
( 8)	. 0124
( 9)	. 0301
(10)	. 0077
(11)	. 0098
(12)	. 0156
(13)	. 0220
(14)	. 0313
(15)	. 0636
(16)	. 0247
(17)	. 0121
(18)	. 0107
<hr/>	
18)	. 3454
<hr/>	
. 0192 average.	

Notice that sometimes the loss amounts to six hundredths of a cubic centimeter, that is as much as 1.5 per cent.

*The loss in the syringe.*—The water that was drawn up into the syringe is now emptied into another carefully weighed graduate and the added weight determined. The difference gives the total loss, and the difference between the total loss and the loss in the graduate gives the loss in the syringe.

As much as possible of the contents of the syringe is pressed out by means of an air cushion behind the column of water. However, as will be seen by the figures, an appreciable amount remains behind; especially if the syringe has a shoulder or a poor packing presenting a large wetted surface.

The following figures give the result of eighteen weighings to determine the loss in the syringe:

Loss in the syringe.	
( 1)	0. 0219 A special syringe, "Sub Q" joint, no shoulder.
( 2)	. 0097 A special syringe, "Sub Q" joint, no shoulder.
( 3)	. 0295 A special syringe, "Sub Q" joint, no shoulder.
( 4)	. 0307 A special syringe, "Sub Q" joint, no shoulder.
( 5)	. 0147 A special syringe, "Sub Q" joint, no shoulder.

Loss in the  
syringe.

( 6)	0. 0272	A special syringe, "Sub Q" joint, no shoulder.
( 7)	. 0224	A special syringe, "Sub Q" joint, no shoulder.
( 8)	. 0315	A special syringe, "Sub Q" joint, no shoulder.
( 9)	. 0119	A special syringe, "Sub Q" joint, no shoulder.
(10)	. 0232	A special syringe, "Sub Q" joint, no shoulder.
(11)	. 0401	A special syringe, "Sub Q" joint, no shoulder.
(12)	. 3363	Colin syringe with old packing.
(13)	. 0871	Colin syringe with old packing.
(14)	. 0276	New Colin syringe.
(15)	. 0855	New Colin syringe.
(16)	. 0747	New Colin syringe.
(17)	. 1153	New Colin syringe.
(18)	. 0969	New Colin syringe.

---

 18) 1. 0862
 

---

. 0603 Average loss in the syringe.

More is lost in the syringe than in the graduate, and the two together make an appreciable amount, in one instance (weighing No. 12) to more than 8 per cent of the amount of fluid used.

*The new method.*—To avoid these errors, the amount of fluid which the animal is to receive is now measured directly into the barrel of the syringe, thereby totally eliminating the loss in the graduate; and the fluid remaining in the syringe after it is emptied, is washed out with sterile salt solution or other suitable fluid which is then injected into the animal, so that the loss, if any, is not appreciable.

The syringe used for carrying out this technique is a modification of the old Koch syringe. The glass barrels for the syringe were made for me by the Randall-Faichney Company, of Boston, who mold a thread in the glass on the end of the barrel so that the needle screws directly upon the glass. This is a distinct advantage and has many points to recommend it over the old slip joint, particularly in that the joint is very tight, and no amount of pressure can force the needle from its bearings.

The bulb was made for me by Lenz & Lossau, of Washington, D. C., and as will be seen by reference to the illustration, differs from the Koch pattern in that there is no stopcock. The soft rubber stopper fits into the syringe like the cork in a bottle (see fig. 2) and is adjusted more readily than the ground glass and metal cap of the Koch syringe.

Note that the barrel tapers gradually to the needle so that the last drop will readily run out. The top has a slight flange which is handy in holding the syringe in use.

These slight modifications in the construction of the syringe are intended to facilitate its use as well as to increase its accuracy. The way of using these syringes differs so manifestly from any known to me that I will describe it in detail, for the precision depends as much upon the method of using them as upon their construction.

The glass barrels are cleaned in a saturated solution of chromic acid in sulphuric acid which leaves them chemically clean and prevents water or other fluids sticking to the glass in large drops. The acid is thoroughly washed out with tap water and then flushed in distilled water, allowed to dry and sterilized by dry heat. Clean glass allows a free flow, diminishing the amount of water which adheres to the surface, and thereby helps to thoroughly empty the contents.

The needles are sterilized separately by the usual method of boiling in a 1 per cent sodium carbonate solution.

The needle is now screwed on the barrel of the syringe and the joint tested by drawing some sterile salt solution in and out several times. If the joint is tight and the needle pervious, the outside is dried with a little piece of sterile gauze, and the needle is now plunged into a jar of sterilized albolene. The albolene acts as a temporary plug, preventing any of the fluid which is placed in the syringe from escaping until it is injected into the animal.

The necessary number of syringes are prepared, one for each animal. In testing diphtheria toxin and antitoxin we sometimes have a battery of ten, twenty, or thirty syringes thus prepared, arranged on the rack as shown in the accompanying diagram. (Fig. 1.)

The amount of fluid desired to inject into the animal is now carefully measured directly into the barrel of the syringe. This is injected into the animal, and then without withdrawing the needle the bulb is removed; a few cubic centimeters of salt solution are quickly blown into the barrel, washing down the sides, and this in turn is injected into the animal.

The syringes can not be turned over, as is the case with a piston syringe. It is not necessary, however, to hold them upright, as might at first be imagined. They may be tilted to a greater angle than  $45^{\circ}$  without danger of the fluid running out.

The rack in which the syringes are shown (fig. 1) is made of wood and has several conveniences worth noting. The bottom shelf is of glass. The least drop through the needle or from a leaky joint is plainly seen on the glass, which acts as a telltale against this possible error.

I also write upon the glass plate the amount each syringe is to receive, which helps to avoid mistakes and facilitates the work.

Each glass barrel is numbered with the number of the experiment or of the animal to receive the injection. This is very convenient and avoids confusion.



The syringes are prepared and filled in a special room where the exact measuring is done, and the rack is then found handy to carry the syringes to the animal room, where the work of injection is carried on.

In standardizing diphtheria antitoxin we always inject a total of 4 c. c. of fluid, allowing only one washing, but when the total amount of fluid injected is immaterial, especially in larger animals, the syringe may be washed out several times with a neutral fluid.

In using this method in standardizing diphtheria antitoxin it is important to shake and roll the syringe so as to obtain an intimate mixture of the toxin with the serum.

In working with definite weights of solids the solution may be made in the barrel of the syringe, so that the method is applicable in any sort of work where it is important to inoculate animals with precise amounts.

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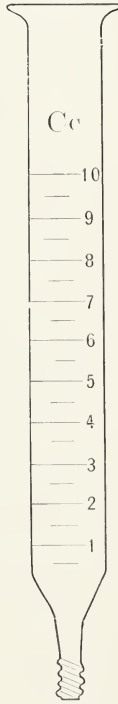
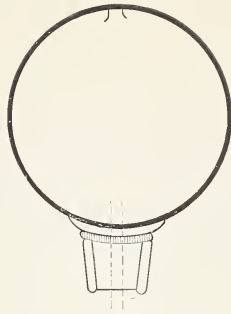


FIG. 2.—SHOWING THE THREE PARTS OF THE SYRINGE, VIZ, THE RUBBER BULB, THE GLASS BARREL, AND THE NEEDLE.



*W. H. Salzberger*

TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 20.

M. J. ROSENAU, Director.

APRIL, 1905.

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A ZOOLOGICAL INVESTIGATION

INTO

THE CAUSE, TRANSMISSION, AND SOURCE

OF

ROCKY MOUNTAIN "SPOTTED FEVER."

BY

CH. WARDELL STILES.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.

1905.

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TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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WALTER WYMAN, *Surgeon-General,*  
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# A ZOOLOGICAL INVESTIGATION INTO THE CAUSE, TRANSMISSION, AND SOURCE OF ROCKY MOUNTAIN "SPOTTED FEVER."

By CH. WARDELL STILES, PH. D.

Chief of Division of Zoology, Hygienic Laboratory, United States Public Health and Marine-Hospital Service.

## SUMMARY.

This paper contains the results of a zoological investigation into the cause, transmission, and origin of the so-called "spotted fever" of the Rocky Mountains and consists chiefly of negative findings.

The disease was first described by Wood (1896), then by Maxey (1899) for Idaho, and by McCullough (1902), Gwinn (1902), Wilson and Chowning (1902, 1903, 1904), Cobb (1902), Anderson (1903), and Gates (1903) for Montana.

It has been known since 1872 in the Bitter Root Valley, but its early history elsewhere seems not to be established. It is known under the various names of "spotted fever," "tick fever," "black fever," "blue disease," "black measles," and "piroplasmosis hominis."

Several suggestions have been made as to the cause of this disease, but the only definite proposition is that advanced by Wilson and Chowning (1902, 1903, 1904), and supported in part, at least, by Westbrook (*a*), Cobb (*a*), and Anderson (*a, b*). According to this theory: (*a*) "Spotted fever" is caused (p. 17) by a protozoon to which the name *Piroplasma hominis* has been given and which infects the red blood corpuscles; (*b*) this parasite is transmitted (p. 20) by ticks (*Dermacentor andersoni*); (*c*) the burrowing squirrel (*Citellus columbianus*) harbors a *Piroplasma* which can not be distinguished from *P. hominis*, and this rodent (p. 24) may perhaps be the original host for the disease.

(*a*) My efforts to find a *Piroplasma* in the fresh blood of 9 cases of the disease in man, and in the stained blood of these and several additional cases, have been negative (p. 19), despite an actual microscopic study of more than 200 hours; Ashburn has had similar negative results; Chowning was unable to demonstrate the parasite to us in the fresh and the stained blood of a typical case; and several investigators who have since examined slides, both from Idaho and Montana cases, have not been able to find the *Piroplasma*. Accordingly, the work of 1904 has failed to confirm the conclusions of 1902 and 1903, and indications are not lacking that at least some of the stages of the supposed *Piroplasma hominis* consist in reality of vacuoles, blood platelets, blood dust, artifacts, and tertian malaria parasites. Wilson and Chowning report that they were able to transmit the disease to rabbits, but I was unable to do this (p. 19).

(b) I have likewise been unable (p. 20) to confirm the hypothesis that this disease is transmitted by ticks, for while there is a certain amount of circumstantial evidence against this arachnoid, one of the fundamental premises of the tick theory (namely, the piroplasmatic nature of the disease) is called into question; and, further, cases are known in which a history of tick bite has not been established (p. 22).

(c) I am unable to see any valid arguments (p. 25) in support of the view that the burrowing squirrel (*Citellus columbianus*) forms the original host for the disease, while I find several arguments against this hypothesis.

Having failed to confirm the piroplasmatic nature of Rocky Mountain "spotted fever" by direct evidence, I attempt to do so by indirect evidence, namely, by comparing the symptoms reported for this disease with those reported for known piroplasmatic maladies; but in this also my work is negative, for while a thin, watery, anemic condition of the blood, a thick condition of the bile, marked emaciation, prominence of hemoglobinuria, practical absence of skin lesions, and the occurrence of the cases in groups (corresponding to the extreme fertility of ticks) are the striking features described for piroplasmosis in animals, "spotted fever" patients present a thickened blood, fluid bile, no marked emaciation (at least so far as reported), little or no hemoglobinuria (Wilson and Chowning), prominent skin lesions, and the occurrence of isolated cases, widely separated. Accordingly, if this disease is a piroplasmosis, *Piroplasma* has an effect in man markedly different from the effect it has in cattle, sheep, dogs, and horses.

Rocky Mountain "spotted fever" is reported for Idaho, Montana, Nevada, Oregon, Wyoming, ?Washington State, and possibly Utah and Alaska (p. 25). About 200 cases are said to have occurred in the Bitter Root Valley since 1872 (p. 29); of these, 139 have been collated, showing a lethality of 70.5 per cent. It is rather striking that the cases seem to be more or less confined to valleys (p. 30), and infection seems to take place chiefly in the foothills. In the Bitter Root Valley the cases occur chiefly on the west side of the river, and are confined to the months of (January) March to September, inclusive; April, May, and June are the worst months. It is rather striking that more cases seem to develop under moist conditions (p. 33), as on the west side of the river, and during or following a rise in the streams caused by rain or melting snow, than under dry conditions; but the significance of this popular view is not altogether clear. Both sexes and all ages (p. 37) are subject to the disease, but it is more common in males from 21 to 40, and in females from 11 to 40 years of age, than at other times of life; the lethality varies, being in the Bitter Root Valley 45.4 per cent for females from 11 to 20 years of age up to 100 per cent for all patients over 60 years old. So far as one can judge, occupation (p. 38) seems to play a rôle, for a very large percentage of the patients are on farms or are connected with the lumbering industry.

In Idaho, a mild type (p. 39) of the disease exists, with a lethality of about 1 to 3 per cent. In Montana, physicians speak of a mild type (without spots), medium cases, and severe, very fatal cases; some men also speak of cases of "localized" spotted fever (p. 39).

About 90 per cent of the cases give a history of exposure to wet or cold (p. 39). The period of incubation (p. 40) is variously given as 2 to 21 days. The attack may be preceded by a few days of malaise, or the onset (p. 41) may be marked by sudden chill, followed by fever, with or without nausea; the disease usually lasts about 10 to 21 days (p. 42); usually only one case occurs in a family (p. 43), but instances are known in which two members of a family are attacked the same day, or within a few days of each other; it is almost universally admitted (p. 44) that the disease is not contagious, but cases are known where contagion does not seem to be entirely excluded.

The patients may assume a position of general flexion in bed (p. 45), and may have a peculiar urinous odor (p. 45) about them.



The most characteristic and constant symptom is the eruption (p. 45), which usually appears first on the wrists, ankles, and back, about second to fifth, chiefly third day, and spreads rapidly over the rest of the body, lasting about 8 to 21 days, or even several months, and after the fever subsides, becoming visible upon exposure to cold or after a warm bath or active exercise; these spots are petechial and not raised; at first they are rose colored, and disappear momentarily upon pressure, but later they become permanent and assume a dark blue or purplish color; they may coalesce and give a mottled or marbled appearance to the skin; they may or may not be tender to the touch. Desquamation (p. 49) begins about the third week. Jaundice (p. 50) is more or less marked, first noticed in the conjunctivæ. There may be cyanosis (p. 50), or—especially on the scrotum, fingers, or toes—gangrene (p. 50). Hyperesthesia (p. 51) is common, and may be intense. The subcutaneous fat (p. 51) remains.

The face (p. 51) frequently shows a congested, bloated, stupid expression. There may be ringing in the ears (p. 51). The eyes (p. 52) are more or less injected. Photophobia (p. 52) is common, and may be very marked. Nosebleed (p. 52) is more or less frequent. Sore throat (p. 53) is more or less common; breath may be offensive. The tongue at first shows a heavy white or yellowish coat, with red tip and edge, and becomes brownish, dry, and cracked as the fever progresses; the teeth may be covered with sordes.

There may be gurgling and tenderness (p. 55) in the right iliac fossa; tympanites may develop. The joints may become swollen.

Loss of appetite (p. 55) is an early symptom, or in some cases the appetite remains good.

Irritability of and pains in the stomach (p. 56) are reported. Nausea (p. 56) is more or less common, and vomiting may be present. Constipation (p. 58) is very common. The liver (p. 58) may be enlarged to some extent. The gall (p. 60) is fluid. Pancreas may be normal in size or enlarged.

Heart sounds (p. 62) are reported as normal. Pulse (p. 63) is usually full and strong at the onset, but gradually becoming more and more rapid, losing in strength and volume; in ordinary cases it may be 80 to 130, and has been reported as high as 150, or even 186. The blood (p. 63) becomes dark and thick; it shows some decrease in the red cells (to 4,100,000 or to 3,558,000) and may show some increase (12,000 to 15,600) in the white cells, the most interesting feature, according to Anderson, being an increase in the large mononuclears; hemoglobin may fall as low as 50 per cent.

The spleen (p. 67) is uniformly enlarged and tender.

The initial chill (p. 68) may be absent, slight, or severe; and chills or chilly sensations may continue more or less throughout the attack.

The fever develops rapidly, and may register 102° to 104° or 105° F. when the patient takes to bed. It gradually reaches its maximum in 2 to 7 days, when it ordinarily registers 103° to 106°. For temperature charts, see Wilson and Chowning, or Anderson, on page 111.

An irritative cough (p. 71) may exist from the first. Respiration (p. 72) is increased, usually to 26 to 40—in some cases 50 to 60. Edema of lungs develops in a number of cases.

There may be great tenderness or soreness of the muscles.

Some cases are exceedingly nervous, symptoms (p. 74) being so prominent as to remind one of cerebrospinal meningitis. Malaise, restlessness, insomnia, hyperesthesia, jactitation, dizziness, headache, pains, "bone ache," tenderness of neck and lumbar region, photophobia, divergent and convergent squint, delirium, coma, convulsions, and in a few cases opisthotonos have been reported. Autopsy fails to reveal any lesions which would justify the diagnosis of cerebrospinal meningitis. Kernig's sign is absent.

The kidneys are often disturbed; they may be enlarged. Bladder (p. 83) normal or nearly so. The urine is reported as reduced in amount, slightly above normal in color to highly colored: specific gravity 1,018 to 1,030; reaction acid, so far as reported; albumen present or absent: sugar and bile not reported: granular, blood, hyaline, and epithelial casts are reported: hematuria and hemoglobinuria absent or slight.

Menstruation is delayed by attack, and abortion is reported for pregnant women.

Several authors refer to relapses, following muscular exertion or exposure to cold.

Hypostatic pneumonia, rheumatism, and gangrene are among the most frequent complications (p. 87) mentioned: pneumonia predominates in frequency.

Convalescence (p. 87) may be rapid or very slow, lasting ten to twelve weeks or even longer.

Prognosis (p. 88) seems to be favorable (lethality about 1 to 3 per cent) in some places (as in Idaho); but it is very unfavorable in others (as in Bitter Root Valley), where cases in which the eruption is marked show a lethality of about 70 per cent. See also under "sex and age," page 37, and "number of cases," page 29.

Death (p. 89) occurs from third to twenty-ninth day, usually from sixth to twelfth day.

Local physicians agree that diagnosis (p. 89) is not difficult, and even the laity recognize the disease on sight: its peculiar geographic and seasonal distribution, endemic character, severe aching pains in the muscles, joints, bones, neck, and head, appearance of nonelevated spots on the second to seventh day, at first rose-colored and on wrists, ankles, and back, disappearing momentarily on pressure, rapidly spreading to entire body, and becoming darker, and then not disappearing on pressure, the frequency of constipation, the coated tongue, accelerated pulse, temperature, icterus, and expression denoting profound intoxication of entire system, lead the local physicians to the diagnosis of "spotted fever."

It is generally admitted that the disease resembles typhus (p. 90) more than it does any other malady; some cases resemble cerebrospinal meningitis (p. 91); compare also typhoid, dengue, peliosis rheumatica, etc., (p. 92).

Satisfactory specific treatment (p. 92) is unknown.

Clinical histories (p. 100) of cases, and a bibliography (p. 116) of the subject are added.

I have no new theories to present regarding the cause, transmission, and origin of this disease.

During the investigations I incidentally found several new species of parasites which I hope to describe soon, and three of which I propose to dedicate to Doctors Anderson, Ashburn, and Buckley.

Date of manuscript, January 14, 1905.

## INTRODUCTION.

Pursuant to orders from the Surgeon-General, dated May 2, 1904, I visited the Bitter Root Valley to study the so-called "spotted fever" ("tick fever," "piroplasmiasis hominis") from a zoological point of view, and remained there from May 7 to July 6, 1904.

The special object of my detail was to trace the life cycle of the parasite (*Piroplasma hominis*) which had been described as the cause of the disease, to study the tick which was supposed to transmit it, and to trace the disease in the burrowing squirrels, in which it was thought to originate. The points at issue, it will be seen, bore more directly upon discovering some method of prevention than upon a study of the symptomatology.

As the seasonal duration of the outbreak is short, and as the parasite

was classified in one of the most difficult groups, from a standpoint of interpretation, I had upon starting little hope that much could be accomplished in one season; in fact, I viewed the trip as the beginning of an investigation which would probably occupy the spring months for a number of years to come.

From the literature which had appeared upon this malady, especially from the last article by Wilson and Chowning (1904a), I had become somewhat prejudiced in favor of the protozoan theory relative to the origin of this disease, and also in favor of the theory that it was transmitted to man by ticks belonging to the genus *Dermacentor*; regarding the hypothesis of its origin in the burrowing squirrel, however, I must confess that a priori reasons made me very skeptical.

During my stay in the Bitter Root Valley I was able to see 10 patients who I was assured by local physicians presented typical cases of the disease. In 9 of these cases I was able to search in the fresh blood for the parasite. Part of my time was occupied in studying the ticks, the burrowing squirrels, the topography of the region, and other points to be considered in connection with the malady.

#### ACKNOWLEDGMENTS.

I am under numerous obligations to various persons, especially the local physicians in the valley, for many courtesies extended to me during my investigations. Among these I would mention the following in particular:

To Dr. John Jay Buckley, who for years past has spent much time and money in studying "spotted fever," I am under special obligations for the courtesies of his private laboratory and library, as well as for giving me so much time in showing me through the valley, taking me to see patients, and for other courtesies too numerous to mention.

To Dr. Percy M. Ashburn, captain and assistant surgeon, U. S. Army, stationed at Fort Missoula, I am under many obligations for use of his laboratory and his instruments, for accompanying me on various trips through the valley, and for his association in studying the cases. Doctor Ashburn had commenced to study "spotted fever," under instructions from Surgeon-General Robert M. O'Reilly, U. S. Army, before I reached Missoula. After my arrival we worked together, yet independently, constantly checking and criticising each other's work. Our final conclusions were practically identical in all important respects.

To Maj. Z. W. Torrey, in command of Fort Missoula, I am indebted for many official courtesies, including the use of post transportation facilities upon several hard trips through the mountains.

To Dr. Edward W. Spottswood, chief surgeon of the Northern Pacific Railroad Hospital at Missoula, I am indebted for the use of his laboratory and laboratory supplies, as well as for valuable advice.

To President Oscar J. Craig and Prof. M. J. Elrod, of the State University, I am indebted for the use of the university laboratories and supplies. Professor Elrod also kindly took photographs of patients at my request and accompanied me on collecting trips.

To Dr. William Park Mills, Dr. Charles H. Pixley, Dr. Russell Gwinn, Dr. Samuel W. Minshall, Dr. George Hampton Putney, Dr. William B. Parsons, Dr. John T. Brown, Dr. Thomas A. Fitzgerald, Dr. George T. McCullough, Dr. Watkins, Dr.



William A. Glasgow, and Dr. Joseph A. Tremblay (all of Missoula), to Dr. Brice and Dr. E. A. Brooke (of Stevensville), to Dr. Thomas H. Hanbidge (of Victor), and to Dr. J. W. Howard and Dr. George McGrath (of Hamilton) I am indebted for the privilege of seeing actual and suspected cases of "spotted fever," for information, advice, and various other courtesies.

To Sister Superior Gasper, Sister Gabriel, Sister Ignatius, Sister Wilfred, and the other sisters of St. Patrick's Hospital I am indebted for the many courtesies they extended to me at the hospital.

To Doctors Louis B. Wilson and William B. Chowning, of Minneapolis, I am indebted for one of their original slides and for various points of information. I also had the pleasure of personal association with Doctor Chowning for two weeks in Missoula, where we examined a case together.

To Dr. L. A. Gates, of Bridger, Mont., I am indebted for an interesting account of 4 cases of "spotted fever" which he treated, and a table of all 17 cases which have come to his notice.

Last, but not least, I am indebted to Dr. Thomas D. Tuttle, secretary Montana State board of health, for his cordial cooperation and advice.

The fact that I did not accomplish more than I have to report lies in the difficulties of the subject and the shortness of the season, and not in any lack of facilities which it was in the power of the local authorities and profession to offer me.

#### HISTORICAL REVIEW OF LITERATURE.

For a proper understanding of the subject of this report it will be well to give extensive historical reviews of various phases of the matter at hand, more especially as no one has as yet collected all of the observations reported.

The first printed account of this "spotted fever" which I have been able to trace is a summary given by Lieut. Col. W. M. Wood (1896, pp. 60-65), Deputy Surgeon-General (retired), U. S. Army, at Boise Barracks, Idaho. He himself had seen no cases, but he collected statements regarding the disease in Idaho from Drs. L. C. Bowers, George Collister, J. K. Dubois, R. M. Fairchild, D. W. Figgins, W. D. Springer, C. L. Sweet, and H. Zipf. The discussions are mainly of symptomatology and will be considered in detail in that part of the present report.

Maxey (1899, pp. 433-438) presented before the Oregon State Medical Society an excellent paper on the disease as found in Idaho. He discussed its seasonal and topographic distribution, symptoms, specific and differential diagnosis, prognosis, and treatment. He is of the opinion that "spotted fever" of Idaho is "an independent, specific disease, and related in no way to any disease described in our text-books on practice."

Commenting editorially upon Maxey's paper, the Medical Sentinel (1899, pp. 456-458), of Portland, Oreg., expressed the view, based solely upon the symptomatology, that "this spotted fever bears a closer resemblance to the papular form of erythema exudativum multiforme than to any other known morbid entity."

McCullough (1902, July, pp. 225-228) presented a paper on "spotted fever" before the Montana State Medical Society at Anaconda, Mont., May 21, 1902. He discussed the distribution of the malady, seasonal occurrence, symptoms, complications, prognosis, treatment, and its name.

In the same number of the same medical journal in which McCullough's paper was printed, there appears a summary of results obtained by Wilson and Chowning (1902c, pp. 238-239), who claim to have found a parasite in the red-blood corpuscles which resembles the parasite of malaria. They think that evidence points to some kind of a tick as its transmitter.



Gwinn (1902) presented a paper on "spotted fever" before the Montana State Medical Society, at Anaconda, May, 1902. He discussed the various possible modes of infection, gave very brief observations on two autopsies, an excellent account of symptoms, diagnosis, prognosis, and treatment. This paper was published in the *Missoulian*, a daily paper issued in Missoula, but I have been unable to find it in any medical journal.

Wilson and Chowning (1902a, 1902b) investigated this disease for the Montana State board of health. Doctor Wilson reached Missoula on May 16 and Doctor Chowning on May 26. On July 1 they dated a preliminary report which was printed on July 19. Wilson and Chowning reached conclusions which, if correct, are of far-reaching importance. They give a summary of the results obtained upon 6 autopsies. The most important points in the paper are those dealing with the etiology, transmission, and origin of the disease. Briefly stated, these points are as follows: No bacteria of etiologic significance were obtained in any case, but in stained coverslip preparations of (1902) cases 2 to 6 they found certain ovoidal bodies within the red-blood cells; the nature of these bodies was not clear until they examined the fresh blood of case 7: "Intracellular parasites, showing ameboid movements were found. In several of these observations extracellular forms were also found. \* \* \* Probably not more than 1 red cell in 500 in the circulating blood is ordinarily infected." They describe 3 phases of the parasite, which they claim to have transmitted experimentally to rabbits.

The final point they make is that the common gray spermophile (*Citellus columbianus*) possibly forms the regular host for the parasite they found in man.

The views regarding the tick transmission and the origin of the disease in the spermophile are advanced as "hypotheses."

Cobb (1902, pp. 1868-1870) visited the Bitter Root Valley in June, 1902, where he found Wilson and Chowning already at work. His report contains a brief account of the Wilson and Chowning observations. Cobb was in the valley too short a time to thoroughly confirm or refute the Wilson and Chowning hypotheses, but from what he saw it is clear that he was favorably impressed by their views.

On December 31, 1902, Wilson and Chowning (1903a) finished their more complete report to the Montana State board of health.

The paper contains a discussion of the history of the disease, a list of 114 cases they compiled (chiefly from correspondence with local physicians), location, season, table of distribution of cases by months, previous condition of patient, sex and age of patient, types of the disease, clinical histories and autopsy notes of the cases they observed in 1902, a case of "local infection," an excellent general summary of symptoms, morbid anatomy and histology, etiology, "hæmatozoa of spotted fever," inoculation experiments, mode of infection, the gopher as possibly the normal host of the hematozoon, and suggestions relative to future investigations. It is important to note here that at the conclusion of their article they say:

"While the tick-gopher hypothesis is a very alluring one, it must not be forgotten that as yet but few positive facts have been obtained for its establishment. Aside from the collection of clinical evidence attempts must be made to transfer hæmatozoa from infected gophers by direct blood inoculations and through tick bites to various uninfected animals, as the rabbit. A comparison of the results of such inoculations, if successful, with similar inoculations from human cases (see No. 3) should give valuable data as to the identity or dissimilarity of the protozoa from gophers and those from man. In view of the high mortality of 'spotted fever,' it will probably be impossible to get any man to submit to a direct blood inoculation, or tick bite, from patients as has been done recently with yellow fever. But it seems probable that all that is necessary may be done by careful inoculation along the lines here indicated."

During the season of 1903, at the request of the Montana State board of health,

Doctor Anderson investigated the disease on behalf of the Public Health and Marine-Hospital Service, and Doctors Wilson and Chowning continued their studies on behalf of the Montana State board of health.

Anderson (1903c) introduced into medical literature the name "tick fever" for this disease, accepting the tick as the "very probable and almost proved" method of transmission. He reprinted the Wilson and Chowning map of distribution in Montana and added a general map of the States in which the disease is reported. He discussed the geographic distribution, climate, season, occupation of patients, their age and sex, the parasite, and reprinted the list of cases published by Wilson and Chowning, bringing it down to 1903; he discussed method of infection and the symptomatology, gave clinical histories of some of the 1903 cases, with clinical charts and blood counts, autopsy notes, morbid anatomy, prognosis, diagnosis, and treatment. He did not mention the spermophile theory advanced by Wilson and Chowning (1902, 1903), but accepted certain phases of the parasite of man described by Wilson and Chowning as "very probably the cause of spotted (tick) fever."

Gates (1903) gave clinical reports of two cases.

In their third paper, Wilson and Chowning (1904a) cover much the same ground discussed in their second publication (1903a), adding some new observations and omitting the detailed clinical reports. They apparently definitely accept the parasite, which they now name *Piroplasma hominis*, as the cause of the disease, but they still speak of the idea of tick transmission as an "hypothesis."

Since the appearance of this paper, a number of text-books and medical journals have referred to their work and have accepted it, at least to some extent. Manson (1903, pp. 174-176), however, points out that the experimental proof of the Wilson and Chowning hypotheses is lacking, and Nuttall (1904, p. 221) remarks that in "spotted fever" the symptoms differ markedly from those observed in the bovine, ovine, equine, and canine [piroplasmatic] maladies, but he admits (p. 252) that the 1904 paper by Wilson and Chowning is much more convincing than their former articles, so far as the parasite is concerned. Manson (1903) and Nuttall (1904) correct the name of the parasite to *Piroplasma hominis*.

In August, Stiles (1904, pp. 1649-1650; 1904, pp. 362-363) published a preliminary report upon investigations conducted during the spring of 1904.

October 31, 1904, Ashburn delivered an address upon "spotted fever" before the Cincinnati Academy of Medicine. This has not yet been published, but it gave rise to a rather vigorous editorial by Heidingsfeld (1904, pp. 492-493) who attacked the Wilson and Chowning hypotheses.

Craig (1904, pp. 1016-1017) had no opportunity to examine slides of "spotted fever" blood, but he came to the conclusion that the objects described as *Piroplasma hominis* "were not due to the presence of a parasite, but to certain changes, especially in the hemoglobin of the red cells, produced by the disease." He claims to have observed appearances, coinciding in every particular with the description given by Wilson and Chowning, and Anderson of *P. hominis*, in a large number of diseases, especially in fevers, such as typhoid, malaria, smallpox, measles, grippe, and frequently in pneumonia and tuberculosis.

In the Middleton-Goldsmith lecture (Nov. 30, 1904), before the New York Pathological Society, Stiles (1905, pp. 9-21) discussed his results more in detail than given in his preliminary report.

#### DEFINITION.

*Idaho*.—Dubois (1896, p. 64) characterizes "spotted fever" as an "acute, febrile, eruptive disease, noncontagious but epidemic, found chiefly in March and April."

Fairchild (1896) speaks of it as a "fever of typhoid type, self-limited, and characterized by a red eruption over whole body."

Springer (1896, p. 61) refers to it as a "continued fever, with typhoid condition and a red eruption general over entire body."

Sweet (1896, p. 61) defines it as a "continued fever, with mild exacerbations; temperature usually not excessive. Cases sometimes pass into an adynamic or typhoid condition."

Maxey (1899, pp. 432-433) defines spotted fever as "an acute, endemic, noncontagious, but probably infectious, febrile disease, characterized clinically by a continuous moderately high fever, severe arthritic and muscular pains, and a profuse petechial or purpurial eruption in the skin, appearing first on the ankles, wrists, and forehead, but rapidly spreading to all parts of the body."

*Montana.*—Gwinn (1902) defines this disease as "an acute, febrile, noncontagious affection, characterized by an eruption of macules which are at first pink, afterwards gradually assuming a purplish or dark blue color."

### HISTORICAL REVIEW OF THE DISEASE.

*Idaho.*—"Spotted fever" has been known in Idaho for about thirty years (Wilson and Chowning, 1902a, p. 132; Anderson, 1903c, p. 8).

*Montana.*—According to McCullough (1902, p. 225), "spotted fever" has prevailed in various degrees of intensity in Bitter Root Valley from the earliest history of its settlement by white inhabitants; he states that prior to that time there is convincing evidence that the Indians were also subject to this ailment. Gwinn (1902) states that according to his personal knowledge it has been prevalent in the Bitter Root Valley since 1886, and he is credibly informed that it has existed there since the region was first settled by white men; he adds that the number of cases has of course increased with the number of inhabitants.

Wilson and Chowning (1902a, p. 132; 1903a, p. 28; 1904a, p. 33) report that so far as can be determined the first case of "spotted fever," "black fever," or "blue disease" in the Bitter Root Valley occurred in 1873 (this case—J. W.—occurred in May, near Woodside). At this time there were but few white men in the valley. No authentic information of its occurrence among the Indians, who until 1890 inhabited the valley, has been obtained, though many old residents, including Indians, white trappers, traders, and Catholic priests, were consulted (1903a, p. 28; 1904a, p. 33). It has been recognized as a clinical entity by the local physicians for fifteen or twenty years (1902a, p. 131; 1903a, p. 28; 1904a, p. 31). Anderson (1903a, p. 506; 1903c, p. 8) states that it has been known in the Bitter Root Valley for about twenty years.

In addition to the case in 1873 reported from Woodside by Wilson and Chowning (1903a, p. 28), I might add that Doctor Parsons has kindly called my attention to a second case which occurred at another place in the valley in the same year.

Doctor Buckley, who has spent considerable time and money in tracing back the history of the disease, assured me that he had been unable to obtain any convincing evidence that the Indians had suffered from "spotted fever."

That this disease has existed for some years in other localities than Idaho and the Bitter Root Valley does not seem to be entirely excluded, for the medical history of many parts of the Northwest is as yet unwritten, and there will naturally always remain some cases of disease among the early settlers which will probably be unrecorded and unexplained. To assume that "spotted fever" has made a sudden



spring within the last few years from the Bitter Root Valley to other parts of Montana (as Bridger and Livingston) and to Wyoming is probably not fully warranted in our present knowledge of this malady, for whether these localities actually represent newly infected foci or only newly recognized foci can be definitely determined only by a more complete medical history of these places than is published at present.

#### NAMES OF THE DISEASE.

*Idaho.*—In Idaho the disease under discussion is generally spoken of as “spotted fever,” because of its eruption, and Maxey (1899, p. 434) states that he knows of no other or better name for it; he adds that, although confusing to physicians unacquainted with the affection, this name admirably describes the disease from a lay standpoint, and very probably will be retained in use by the local profession until future research enables us to classify it where it belongs. Dubois (1896, p. 64) says that *Exanthesis rosalia anthrodymia* more nearly expresses the disease than does “spotted fever.” The Medical Sentinel (1899, p. 458) remarks editorially that “the opinion of the writer, based solely upon the symptomatology, is that this spotted fever bears a closer resemblance to the papular form of erythema exudativum multiforme than to any other known morbid entity.”

*Nevada.*—In Nevada this disease is known as “spotted fever.”

*Montana.*—According to McCullough (1902, p. 225) it has been called “black fever” and “blue disease,” probably on account of the dusky or bluish appearance a short time before death of those afflicted. He considers the name “spotted fever” a good one, because to the laity it abodes grave responsibility; \* \* \* “many of the cases terminating fatally with the best skill and untiring energy an intelligent physician can give them, we feel the burden is somewhat lightened, and the responsibility is shared by the family and friends if they are prepared for the inevitable.” \* \* \* Crain (see Wilson and Chowning, 1902a, p. 33) states that in 1891 the disease was called “black measles” by the valley physicians. Wilson and Chowning (1902a) refer to the malady as the “so-called ‘spotted fever’ of the Rocky Mountains,” but remark (1903a, p. 27) that the name “spotted fever” as applied to it is an unfortunate one, since it has been applied to several other diseases.

Anderson (1903a) proposes the name “tick fever,” on account of the relation of the tick to the spread of the disease, and because of the fact that there are already two diseases of man sometimes called “spotted fever.” Wilson and Chowning (1904a, p. 31) state that the name “tick fever” [also frequently “wood-tick fever”] was proposed by the local newspapers when the hypothesis of transmission by ticks was advanced by them in 1902; that it seems fairly distinctive, but is open to the objection that it has been previously used as a synonym of “Texas fever” in cattle,<sup>a</sup> and that it does not accurately indicate either symptoms or etiology; since “spotted fever” appears to be the first described infection of man attributed to a “*Pyroplasma*” [namely *Piroplasma*], they classify the malady as “*Pyroplasmosis hominis*” [namely *Piroplasmosis hominis*]. Nuttall (1904, p. 221), in referring to the investigations by Wilson and Chowning, uses the term “human piroplasmosis.”<sup>b</sup>

#### HISTORICAL REVIEW OF INVESTIGATIONS.

For a number of years this disease has been subjected to study by the local physicians in the regions in which it occurs. Maxey, Gwinn, McCullough, and Gates have published their ideas and it is to be

<sup>a</sup> Not to be confused with the African so-called “tick fever” of man, supposed to be transmitted by *Ornithodoros savignyi*.

<sup>b</sup> Not to be confused with “Dum Dum fever.”



greatly regretted that other local observers, as Buckley, Mills, Spottswood, Brice, Howard, etc., have not published their many valuable observations.

Dr. Emil Starz, of Helena, State bacteriologist and chemist, Doctor Traphagen, of Bozeman, Doctor Strain, of Great Falls, and Doctor Longeway, then secretary of the Montana State board of health, visited the Bitter Root Valley in the spring of 1902. "After going over the ground, examining the character of the soil, water supply, etc., it was determined that none of these conditions was probably responsible for the disease, and that the investigations should be carried on by pathological and bacteriological examinations of existing cases." In accordance with this conclusion, the State board of health invited Drs. Louis B. Wilson and Wm. M. Chowning, of the Minnesota State University, to study the malady.

Wilson was in the Bitter Root Valley from May 16 to July 14, 1902, and April 22 to May 20, 1903. Chowning was in the same district from May 26 to July 14, 1902, and from May 19 to June 19, 1903. He also visited the valley again, on an unofficial trip in June, 1904, spending about two weeks in Missoula.

Dr. J. O. Cobb, of the U. S. Public Health and Marine-Hospital Service, and Prof. F. F. Wesbrook, of the Minnesota State University, spent the last week of June, 1902, in the Bitter Root Valley, studying the disease.

Dr. J. F. Anderson, of the United States Public Health and Marine-Hospital Service, was in the same locality from May 1 to 30, 1903, when he studied the same cases observed during the same time by Wilson & Chowning.

Dr. Percy M. Ashburn, captain and assistant surgeon, U. S. Army, stationed at Fort Missoula, had an opportunity to observe some features of the disease in 1903, but it was not until the season of 1904 that he undertook a more thorough investigation of the malady.

I arrived at Missoula May 7, 1904, and remained in the Bitter Root Valley until July 6, 1904, studying the cases which occurred during that time.

#### SPECIFIC CAUSE OF SPOTTED FEVER.

Various different theories have been advanced regarding the cause of "spotted fever." Among these the following may be mentioned:

*Idaho.*—The vera causa is probably of a teluric character (Bowers, 1896, p. 63). Dubois (1896, p. 64) frankly admitted that as yet no cause can be assigned. Figgins (1896, p. 64) states that he never saw any cases except among people who had used water from creeks and surface wells. He has seen it in families who used water from springs and where the entire family had the disease. Springer (1896, p. 62) gives the cause as probably "water; sepsis." Sweet (1896) says that while there are indications which seem to point out this particular affection as a water-borne disease, there are other circumstances which militate against this theory and are in favor of its being akin to malaria, in that it is frequently seen in persons who have been living in the vicinity of newly broken ground, post holes, plowed ground, and in those who have drunk from seepage water from worked soil, etc. Zipf (1896, p. 65) attributes it to malaria. Maxey (1899, p. 434) concludes that the disease "is, in all probability, caused by some peculiar organism, possibly a miasm, though no specific cause has yet been discovered."

*Montana.*—Gwinn (1902) says that all kinds of theories have been advanced, none of which have been based upon pathological investigations; and none of the theories

are to his mind convincing. McCullough (1902, p. 225) refers to the locality as having a "bearing upon this deplorable affliction with suitable environments, most cases giving a history of exposure to wet and cold, or violent physical exercise and over-exertion."

Wilson and Chowning (1902a, 1903a, 1904a) were the first authors to describe a specific organism as cause of the disease. They call special attention to the fact that their bacteriologic cultures failed to show any bacteria of etiologic significance, and they describe bodies which they interpret as protozoa and which they later name "*Pyroplasma hominis*" [namely *Piroplasma hominis*]. The secretary of the Montana State board of health (see report, issued 1903, p. 25) says that the cause has been "attributed to various sources, particularly the water, mineral, and general conditions of the soil, and by some thought to be contained in the snow of the Bitter Root Mountains, as well as various and varied local conditions."

The only definite proposition as to a specific cause is that advanced by Wilson and Chowning (1902a, c, 1903a, 1904a), namely, that "spotted fever" is due to a protozoon parasite which lives in the red blood corpuscles; this protozoon they classify (1904a) as a member of the genus *Piroplasma*.

The genus *Piroplasma*, which is very possibly identical with *Babesia*, seems very clearly to be a protozoon, but its more exact systematic position is at present somewhat uncertain. It is one of the most difficult of all the protozoa to interpret, and little is known of its life cycle. Its synonymy is as follows:

#### Genus PIROPLASMA Patton, 1895.

1888. ? *Hæmatococcus* Babès [not Agardh, 1828].

1893. *Pyrosoma* SMITH and KILBORNE [not *Pyrosoma* Péron, 1804], type species, *P. bigeminum* of Texas fever.

1893. ? *Babesia* STARCOVICI, 1893, July 1, type *Babesia bovis* (of bovine hemoglobinuria), whose identity with *P. bigeminum* is not fully established.

1895. *Apiosoma* WANDOLLECK [not *Apiosoma* Blanchard, 1885], equals *Pyrosoma* Smith and Kilborne, 1893, renamed, hence type species *P. bigeminum*.

1895. *Piroplasma* PATTON, equals *Pyrosoma* Smith and Kilborne, 1893, renamed, hence type species *P. bigeminum*.

1904. *Pyroplasma* WILSON and CHOWNING, for *Piroplasma*.

In view of the comparatively slight knowledge of the present day relative to the structure and life cycle of the members of this genus, hence the uncertainty as to whether *Babesia bovis* is really congeneric with *Piroplasma bigeminum*, I retain the name *Piroplasma* in this discussion. Should it be demonstrated that *P. bigeminum* and *B. bovis* are congeneric it will of course be necessary to reject the name *Piroplasma* in favor of *Babesia*.

In the genus *Piroplasma* several species are at present known as cause of serious diseases. Thus:

*Piroplasma bigeminum* (Smith and Kilborne, 1893) is the cause of Texas fever of cattle.

*Babesia bovis*, which may be generically identical with, but specifically distinct from, *P. bigeminum*, is accepted as the cause of hemoglobinuria in cattle.

*Babesia ovis* or *Piroplasma ovis* is viewed as the cause of carceag, also known as ovine piroplasmosis.

*Piroplasma equi* is viewed as the cause of equine piroplasmosis; and

*Piroplasma canis* is accepted as the cause of canine piroplasmosis.

All of these parasites are supposed (see p. 20) to be transmitted by ticks (*Ixodoidea*) and the symptomatology of the diseases is more or less uniform (see p. 39).

*Piroplasma donovani* Laveran has been described as a parasite of man, causing non-malarial splenomegaly (Dum Dum fever; Kala-azar) in warm climates; but very serious doubts arise as to whether this organism is a *Piroplasma*, and a new genus (*Leishmania*) has been proposed for it by Ross.

The structures which Wilson and Chowning have found in "spotted fever" have been named—

**PIROPLASMA HOMINIS (Wilson and Chowning, 1903) Manson, 1903.**

1903. *Pyroplasma hominis* WILSON and CHOWNING in Anderson, 1903a, p. 506.—Wilson and Chowning, 1904a, p. 48.

1903. *Piroplasma hominis* (Wilson and Chowning, 1903) MANSON, 1903, p. 33.—NUTTALL, 1904, p. 252.

1904. *Babesia hominis* (Wilson and Chowning, 1903) CHAUVELOT, 1904, p. 93, in part.

Wilson and Chowning (1902a, pp. 134–135) found structures in the blood of spotted-fever patients which they interpreted as protozoa, but they preferred "to make a fuller study of the life history of the organism before attempting to classify it more definitely than as a hematozoon;" they call attention to its similarity to *Piroplasma bigeminum* and also to the parasite of malaria. For a complete description of this parasite the reader is referred to the articles by Wilson and Chowning (1902a, 1903a, 1904a), Cobb (1902), and Anderson (1903a, 1903c).

Neither Ashburn nor I, in a total of 400 hours of microscopic study of the fresh and the stained blood of typical cases, and in an examination of a typical slide kindly sent to me by Wilson and Chowning, was able to find any *Piroplasma*; and Chowning was unable to demonstrate the organism to us in the fresh and the stained blood of a typical case.

*Inoculations.*—Wilson and Chowning inoculated rabbits with blood of spotted fever patients, both in 1902 and 1903, and they found the parasites in the blood of the experiment animals. In 1904 I inoculated rabbits with the blood of 3 fatal cases, as follows:

Two rabbits inoculated with blood within thirty minutes after death of patient.

One rabbit inoculated with blood taken from arm during life.

Two rabbits inoculated with blood within two hours after death.

The blood of these rabbits was repeatedly examined, but with negative results.

Since the observations of Wilson (in 1902, 1903), Chowning (in 1902 and 1903, but not in 1904), Cobb (in 1902), Westbrook (in 1902), and Anderson (1903) all gave positive results, while observations (in 1904)

by Ashburn and myself gave negative results relative to the presence of a *Piroplasma* in the blood of spotted fever patients, I do not feel justified in going to the extreme of stating that no *Piroplasma* is present; all that I can assert is that I was unable to confirm the earlier results.

#### METHOD OF INFECTION.

*Idaho*.—Fairchild (1896) states that families using water from the same well are not liable to be affected similarly. Maxey (1899, p. 434) refers to the fact, in connection with cases, that the sole water supply came from melting snow; in other words, the patients drank snow water and became sick, "therefore there must be, in my opinion, some specific cause for this disease, either in the soil over which the water runs or in the snow itself."

*Montana*.—Wilson and Chowning (1902a, p. 134; 1903a, p. 68; 1904a, p. 44) state that there are no symptoms or lesions which point to the digestive, respiratory, or genito-urinary tracts as the avenue of infection.

Gwinn (1902), in discussing the method of infection, mentions the possibility of its entrance into the body by means of the respiratory tract, the stomach, and the skin, but he reaches no definite conclusions.

Wilson and Chowning (1902a, p. 37) report Hanbidge's interesting note that case 81 (of 1901) drank no water during the season.

The most important theory which comes up for our present consideration is the

#### TICK THEORY.

Wilson and Chowning (1902a, p. 136) say:

Since there is no suspicion of "spotted fever" ever having been transferred directly from man to man, and since there is no symptomatic or post-mortem evidence of entrance of the disease, either by way of the digestive tract, respiratory, or genito-urinary system, the writers were led to examine the skin for evidence of direct inoculation by the bite of some temporarily parasitic animal. As has been noted above, in each case under observation during the investigation evidence of tick bites was present. But it is true that in the locality in which the cases occur many persons in the spring of the year are bitten by ticks and yet show no symptoms of "spotted fever." However, the following facts would seem to suggest the hypothesis that the disease is conveyed to man by means of this arachnid.

An important point upon which I desire to place considerable stress is that the tick theory is a secondary hypothesis based upon the idea that "spotted fever" is caused by a protozoon. If the *Piroplasma* theory is correct, the tick theory immediately receives a very strong argument in its favor, for other species of *Piroplasma* are known to have ticks as their intermediate host.

Accordingly, when Wilson and Chowning, in 1902, found what they believed to be a parasite similar to the parasite of malaria and also similar to *Piroplasma bigeminum*, the most natural conclusion for them to draw (reasoning on analogy) was that this organism was transmitted either by a mosquito or by a tick. They found arguments against the view that a mosquito formed the intermediate host and arguments in favor of the tick, hence they adopted the tick theory as a "working hypothesis."

From their point of view, especially on account of their microscopic



interpretations, this "working hypothesis" was most natural, and thoroughly justified, and they show (see above, p. 13) that they thoroughly understood that certain experimental studies were called for in connection with this theory.

Arriving in Missoula this season (1904), it required but a few days to see the zoological points involved and to understand that an experiment with ticks and rabbits was the most important work to be considered, especially as the strictly medical side of the disease was less important to me than the zoological features, leading to its prevention. As stated above (p. 19), I injected blood from three patients into rabbits, but failed to convince myself of the presence of any *Piroplasma* in the inoculated rabbits. Not being able, so far as I could see, to transmit the disease to rabbits, my tick experiment on these rodents had no further purpose.

Quite a number of points have been advanced in support of the tick theory. I have considered these arguments in detail, from the zoological point of view, and have prepared a lengthy discussion covering them. There are, however, so many points of difference of findings and opinion between the supporters of the tick theory and myself that three of my friends, to whom I submitted this manuscript for criticism, have felt that the discussion might be open to a possible interpretation which was most foreign to my mind. On this account I have omitted from the manuscript all points except the following:

8. All of the patients, 23, coming under observation during this investigation had been bitten by ticks. In 14 cases a history was given of severe tick bites two to eight days before the onset of the disease. In a number of other cases an apparently clear history of severe tick bites immediately preceding the onset of "spotted fever" was vouched for by the recovered patients or their friends.—Wilson and Chowning, 1904a, page 52.

In connection with this point it will be necessary to refer to some of the cases.

It must be admitted as very striking that so many cases of "spotted fever" have been preceded by a tick bite, still in a region where it is almost exceptional to go into the woods or fields without being bitten by ticks, it is not excluded that this is a mere coincidence. On account of this latter possibility, the greatest reserve should be exercised in order not to draw a "post hoc, propter hoc" conclusion.

As the valley was thoroughly worked up this year (1904) upon the subject of ticks and as people kept a close lookout for anything resembling a tick or a tick bite, negative evidence obtained from the cases of 1904 is of more value than that obtained prior to 1903. Let us therefore turn to a consideration of the cases which occurred in 1904:

*Case 1.*—Mr. R., patient of Doctor Buckley; fatal case. History of 2 tick bites in right inguinal region, each surrounded by an undurated inflammatory zone; patient was apparently infected in Grant Creek, namely, outside of the regular district.

*Case 2.*—E. C., patient of Doctor Buckley; fatal case. History of 3 tick bites April 24, back of the ear; bites caused swelling next day, fever at that time; eruption appeared April 27.

*Case 3.*—Mrs. R. A., patient of Doctor Fitzgerald; fatal case. Mrs. A. positively denied any history of tick bite, but thought she had been bitten by a chicken louse about April 27. On account of the tick theory she was on her guard for tick bites. Every inch of her body, including hair, pubis, and armpits, was carefully examined by the nurses, but no sign of ticks or tick bites was discovered.

*Case 4.*—Mrs. M. S., patient of Doctor Merrick; recovered case. Mrs. S. noticed a tick upon her, but claims that it did not bite her; no sign of tick bite was discovered, but there were parts of her body (perineum) which were not examined.

*Case 5.*—Miss McM., patient of Doctor Mills; fatal case. So far as could be determined, tick bites seem to be excluded in this case. Patient was aware of the tick theory and had been sharply on the lookout for these parasites; she had an unusually delicate and sensitive skin; about three weeks prior to the attack, she found a free tick between her shoulders, but she most positively denied that any ticks had bitten her. Every inch of body was carefully examined by two nurses, but no ticks were found; nor was anything found which could be interpreted as tick bite.

*Case 6.*—Mr. F. W., patient of Doctor Pixley; fatal case. History of tick bites about May 5; had chill May 13.

*Case 7.*—G. M., patient of Doctor Howard; fatal case. History of tick bites.

*Case 8.*—R. K., patient of Doctor Minshall; fatal case. History of tick bites in four places May 14 or 15; tick bites cauterized May 18; chill May 16 or 17.

*Case 9.*—Mr. G. C. F., patient of Doctor Gwinn; fatal case. History of many tick bites which were cauterized with carbolic acid.

*Case 10.*—J. B., patient of Doctor Mills; recovered case. Tick bite was denied in this case. An examination of the body showed a slight wound on one ankle, which might have been due to a mosquito, a thorn, a tick, or something else.

*Case 11.*—Mrs. E., patient of Doctor Mills; fatal case. Tick bites were positively denied. Careful examination of the body showed numerous abrasions, said to be due to mosquito bites which the patient had scratched, but no positive evidence of tick bite was found. This patient and her husband were aware of the tick theory and were prepared to treat the bites

Thus, of the 11 cases which occurred in the Bitter Root Valley 6 patients gave a positive history of tick bites. In none of these cases was the tick determined zoologically, but all specimens were supposed to be *Dermacentor andersoni*. In one of the cases the tick bite was promptly treated with carbolic acid.

In the 5 remaining cases tick bites were denied by the patients and their families. In 2 of these cases, however, it was admitted that ticks had been found crawling on the body. In 1 case the entire body was not carefully examined, but tick bite was denied. In 1 case numerous bites, claimed to be due to mosquitoes, were found. In 1 case a slight abrasion was found which could not be definitely explained. In 1 case it was claimed that the patient had been bitten by chicken lice.

In addition to these Bitter Root Valley cases, I am able to refer to 2 cases reported to me by Doctor Alton:

*Case 12.*—Patient noticed 4 tick bites in vicinity of left elbow about May 3; is positive regarding the presence of the ticks and also positive that he was not bitten by anything else.

*Case 13.*—Tick bite twelve days before illness.

Through the kindness of Doctor Gates I am able to give data regarding 17 cases which he observed:

There is no record of any tick bite in 5 of his cases, which occurred 1 each in 1894, 1898, 1900, 1902, and 1904. Of these only the case of 1904 can be given much if any weight.

In 10 of his cases, namely, 1 each in 1900, 1901, and 1902, 4 in 1903, and 3 in 1904, there was history of tick bite.

Two of his cases (15 and 16) of 1904 are especially interesting in this connection:

The patients were husband and wife. On May 29, the husband (case 15), of Bridger, visited the Clark Fork Canyon, some 60 miles south of Bridger, remaining in that vicinity about four days, during which time he was bitten by ticks in five or six places. About seven days from the time he was first bitten, namely, June 5, he arrived home in Bridger, and felt the first symptoms of the disease. Upon reaching home there were two ticks attached to his body, and these, of their own accord or from friction from the clothes, became detached from the body on June 6, and then bit the wife (case 16). The bites occurred during the night, the ticks being removed and killed by the patient the following morning. Following the removal of the ticks, she applied carbolic acid to the bites. On the evening of June 11 she felt chilly, feverish, and a general malaise, and a fatal attack of spotted fever followed.

In this connection it may be pointed out that Doctor Bradbury mentions another instance where husband and wife "had spotted fever at the same time," and he informs me that the wife was taken sick in the morning, the husband in the afternoon of the same day. Neither one was bitten by ticks, so far as could be established.

Wilson and Chowning (1903a, p. 34) record that cases 45 and 46 were two children, aged 3 and 5 years, apparently brother and sister. They are reported as both sick in June, 1899.

Anderson (1903c, p. 16) reports two cases (113 and 114) where the patients were husband and wife. Doctor Heine has written me that "the wife did occupy the same bed as her husband during the period mentioned," namely, during the prodromal symptoms in her husband's case.

In view of these 8 cases (or 6 cases, omitting the two children), it seems to me that the possibility is by no means excluded that, despite the general experience regarding the noncontagiousness of the disease, such close intimacy as sleeping in the same bed might perhaps result in a transmission of the disease to a healthy individual. At least, it must be admitted that such an explanation would account for case 16 of Gates as satisfactorily as do the tick bites; and it must further be admitted that if the tick bites actually did give the infection the proof is still wanting that such method of transmission was not accidental.

Dr. W. L. Samuels (see below, p. 28) has reported to me the case of a girl in 1904 in which no history of tick bite was obtained upon questioning the patient.

In connection with the subject of ticks I am fortunately in a position



to give some data from Idaho also. Doctor Maxey has written me under date of October 21, 1904, as follows:

In view of the above findings <sup>a</sup> and the further fact that both Doctor McCalla and myself had failed to obtain a history of recent tick bite in a considerable percentage of our cases, we were led to question the theories of Wilson and Chowning even before receiving your letter.

In considering the possibility of infection by ticks it may be remarked that the tick is a very fertile animal, laying hundreds of eggs, and on this account it would be expected on a priori grounds that if "spotted fever" were a tick-borne piroplasmatic disease we ought to find quite a number of cases developing in the locality where one case developed rather than one or two cases each in several widely separated localities (see p. 43). It was the limited number of cases in comparison with the great fertility of the tick which first raised my suspicions against the tick hypothesis.

Tick bites are exceedingly common in the Bitter Root Valley; in fact, *Dermacentor andersoni* is so common that it seems rather strange that all of the patients did not show some history of being bitten by them.

That tick bites are not always of no significance is abundantly demonstrated. Doctor Buckley, for instance, had a patient who was bitten on the arm by a tick; the arm became quite swollen and the man was confined to bed for some days. Doctor Parsons had a patient who showed an extensive lymphangitis following a tick bite. Upon several occasions I have seen lesions from one-fourth of an inch to 3 inches in diameter at the point of the tick bite.

#### THE BURROWING SQUIRREL (*Citellus columbianus*) AS POSSIBLE SOURCE OF SPOTTED FEVER.

So far as I am aware, Wilson and Chowning (1902a, p. 136) were the first to suggest that the burrowing squirrel or spermophile represents the original host of this disease. Their grounds for this suggestion were as follows:

The extreme isolation of cases of "spotted fever," their occasional development in localities removed many miles from the site of any previous case, and the long period existing between the death or convalescence of the last case of any one year before the development of the first case in the following year, would point to the possibility of the red-blood cells of some one of the lower warm-blooded animals being the normal host of the parasitic protozoon in that stage of its cycle not passed within the body of some arachnoid. Of the animals within the infected region, the common gray gopher would probably best fulfill the conditions of such a parasitism.

The writers are at present attempting to obtain data which shall confirm or demolish the above hypotheses.

<sup>a</sup> Namely, the inability of Maxey, Charles E. Simon, and Cole to find any *Piroplasma* in blood smears from Idaho cases.



In their later papers, Wilson and Chowning (1903a, pp. 85-90; 1904a, pp. 53-56) go more into detail regarding their reasons for considering the spermophile hypothesis. Anderson (1903a, c) does not refer to the spermophile theory, this omission being due, as he has informed me, to his absolute rejection of the idea.

Differing as I do with Wilson and Chowning in my results relative to *Piroplasma hominis* and the tick hypothesis, I felt it incumbent upon me to discuss in detail all of the points which have been advanced in support of the spermophile theory, but for the reasons referred to on page 21, with regard to my discussion of the tick theory, I have omitted all the discussion of the spermophile theory also.

## COMPARISON OF "SPOTTED FEVER" WITH PIROPLASMATIC DISEASES OF ANIMALS.

### GEOGRAPHIC DISTRIBUTION.

"Spotted fever" is reported for Idaho, Montana, Nevada, Oregon, Wyoming, (? Washington State), and possibly Utah and Alaska.

Anderson (1903c, p. 8) states that it does not prevail south of 40° or north of 47°, north latitude; it occurs at an average elevation of about 3,000 to 4,000 feet above sea level.

*Idaho.*—According to Bowers (1896, p. 63), the disease is endemic in southern and central Idaho over an area of about 4,500 square miles about Boise City. Dubois (1896, p. 64) gives it as occurring within a radius of 50 miles from Boise. Figgins (1896, p. 64) states that it is found only in valleys of the mountain districts, while Zipf (1896, p. 65) says that it occurs more or less every year in the valleys, very seldom in the mountains. Springer (1896, p. 61) confines it to the Snake River Valley and its tributaries, and Fairchild (1896) confines it principally to the same region. Sweet (1896, p. 61) says that it is found in the entire Snake River basin and its tributaries, much of it being seen along the routes of the Oregon Short Line Railroad. Collister, (1896, p. 62) reports it as extending from Pocatello to Huntington, along the Snake River plains. According to Wilson and Chowning (1904a, p. 34), Maxey's paper describes cases in Idaho mostly along the southern foothills of the Boise mountain. The cases seem to be limited largely to the north side of the Snake River Valley from Seven Devils to Haley, and to occur from the latter part of March to the middle of July. This information may possibly have been obtained directly from Maxey, as I do not find these statements in Maxey's paper.

The statements in reference to Idaho by Wilson and Chowning are based upon Maxey's paper and upon the Wood symposium, while those by Anderson are based upon Maxey.

*Montana.*—McCullough (1902, pp. 225-228) states that careful inquiry shows the disease to be more widely spread than is generally supposed, and that it has prevailed at Camas Prairie, up the Blackfoot, at Phillipsburg, Clinton, Rock Creek, Rattle Snake Valley, and far up the Lo Lo, all regions separate and apart from the supposed infected area in the Bitter Root Valley. He calls special attention to this distribution in order to correct the erroneous idea that the disease is a "bugbear to this particular locality" (Bitter Root Valley). Gwinn (1902) refers to the disease as occurring in the Bitter Root Valley, Rock Creek, and Phillipsburg.

Wilson and Chowning (1902a, p. 132) state that the cases in Montana are confined to the eastern foothills of the Bitter Root Mountains, namely, on the western side of

the Bitter Root Valley in an area from 4 to 10 miles wide and 90 miles long. No case has ever been known to originate in Montana outside of this territory, except 7 cases in an area about half a mile wide and 2 miles long in the narrow canyon of Rock Creek, about 20 miles east of the Bitter Root Valley. Later (1903a, p. 42) they modify this statement to read that "few, if any, cases have ever been known to originate in Montana outside of this territory, etc." Still later (1904a, pp. 33-34) they say that the cases in Montana are confined to the eastern foothills of the Bitter Root Mountains, but they refer also to 8 Rock Creek cases and to 2 cases in a valley near Bridger, Mont., about 250 miles east and 75 miles south of Bitter Root Valley. These latter cases are evidently those reported by Gates (1903, pp. 48-51) at Thermopolis (Wyo.) and near Bridger (Mont.).

Anderson (1903a, p. 506) mentions the disease in Montana, particularly for the Bitter Root Valley (from Lo Lo to Como) and Rock Creek, but later (1903c, p. 4) refers also to Gates's cases near Bridger.

During the season of 1904 I observed (through courtesy of the attending physicians) 10 of the 11 cases in the Bitter Root Valley, distributed as follows:

*Case 1.*—Supposed to have become infected at or near a sawmill on Grant Creek, 6 miles north of Missoula; this was reported as being the first case in that locality. Patient was taken to Missoula.

*Case 2.*—Patient infected 3 miles west of Victor, on west side of Bitter Root River.

*Case 3.*—Near Carlton, on west side of Bitter Root River. Patient was taken to Missoula.

*Case 4.*—In Pattee Canyon, on east side of Bitter Root River, 3 miles east of Fort Missoula. There is no evidence that the patient had visited the west side.

*Case 5.*—Near Woodman, up the Lo Lo Creek, west side of Bitter Root River. Patient was taken to Missoula.

*Case 6.*—Supposed to have become infected at Harvey Creek, about 20 miles east of Florence.

*Case 7.*—About 8 miles southwest of Hamilton; on west side of Bitter Root River,

*Case 8.*—Taken sick in Missoula; had not recently been up on the west side of the Bitter Root River, but had visited Bonner, east of Missoula, just prior to illness.

*Case 9.*—Near Florence, west side of Bitter Root River. Patient taken to Missoula.

*Case 10.*—Left Iowa six weeks previously; had been in Bozeman five weeks; arrived in Missoula June 2, changing cars en route to Hamilton; began to feel indisposed about the time he changed cars; taken worse in Hamilton (east side of Bitter Root River); later taken to Missoula.

*Case 11.*—Had been in the United States four weeks; came to Missoula about June 1; remained here five days, then moved to a ranch near Woodman, up the Lo Lo Creek, west side of Bitter Root River. Patient taken to Missoula.

From this will be seen that of the 11 cases in question 6 cases, Nos. 2, 3, 5, 7, 9, 11, appear to have become infected on the west side of the Bitter Root River, while 5 cases show no history of having visited that locality (except case 10, see below, p. 27) immediately prior to infection. One case (No. 4) appears to have become infected on the east side of the Bitter Root River. One case (No. 1) seems to have been infected up Grant Creek. One case (No. 6) appears to have been infected on the west side of Harvey Creek some distance east of the Bitter Root River. One case (No. 8) seems to have become infected either at Bonner or at Missoula; and one case (No. 10) seems to have become infected somewhere between Bozeman and Hamilton, going

via Missoula. From Fort Missoula to a point between Woodside and Hamilton the train runs close to the river on the west side of the stream.

While the predominance of cases on the west side of the Bitter Root River, as reported by Wilson and Chowning and by Anderson, was noticed (6:5) in the season of 1904, the cases were not so confined to that locality as might be expected in view of former statistics. In regard to case No. 6 (Harvey Creek) it is important to note that Wilson and Chowning (1903a, map) report cases Nos. 13, 14, 15 (28 and 30 marked as doubtful), 29, 74, and 107 from the vicinity in which case 1904:6 is supposed to have become infected.

Gates (1905, p. 114) reports 13 cases in or near Bridger from 1900 to 1904, inclusive, 4 of these occurring in 1904.

Alton (1905, p. 110) reports 2 cases in Livingston for 1904; one of these came from Lewiston, the other from Gardiner, Park County.

According to a newspaper clipping dated May 23, 1904, there was a case of spotted fever in Billings, Mont., attended by Doctor Clark.

I have also heard of one case at Dillon, but do not recall the details.

*Wyoming.*—Gates (1903, p. 48) reports 1 case from Thermopolis; see also Anderson (1903c, p. 4).

According to Wilson and Chowning (1904a, p. 34), Dr. J. J. Bradbury, of Cody, wrote to them that cases occurred in 1903 near Cody and Meeteetse. Anderson (1903c, p. 8) also refers to these cases.

Gates (1905, p. 114) reports, in all, 4 cases for Wyoming, namely, Meyersville, 1 case, 1894; Thermopolis, 2 cases, 1898, and Shoshone River, 1 case, 1901.

Bradbury has written to me (October 31, 1904) that he had had 2 cases at Cody, but none in 1904.

*Nevada.*—Maj. W. P. Kendall, surgeon, U. S. Army, reported in a letter to Wilson and Chowning (1904a, p. 34) that he saw cases in 1887 in the Quinn River Valley. Kendall's cases are also referred to by Anderson (1903c, pp. 7-8).

Major Kendall has written to me under date of October 23, 1904, that during his tour of duty at Fort McDermitt, Nev., 1885-1889, he saw 10 or 12 cases of the locally so-called "spotted fever;" his medical friends at Winnemucca, Nev., told him that there was a great deal of this disease at a small hamlet some 25 miles distant up the valley, but by them it was not considered to be a dangerous malady, as "they never died." One of the Winnemucca physicians stated that he had seen some 50 cases.

Dr. P. I. Mangano, of Winnemucca, has written to me under date of November 5, 1904, that he has repeatedly heard of a disease termed "spotted fever" that has appeared at Paradise Valley, some 45 miles distant from Winnemucca, and also at Fort McDermitt, but no case was reported in 1904; he is informed that the disease has appeared at isolated places subsequent to sheep shearing, and many persons sup-



pose it to be due to contamination from the sheep; in many cases the patients are very sick, the attack lasting several months; some fatal cases have occurred.

Dr. W. L. Samuels, of Winnemucca, has written to me under date of November 14, 1904, that "spotted fever" makes its appearance from time to time in Paradise and in a locality near the sink of Quinn River. Both of these localities are sheep countries, and the presence of bands of sheep is supposed to pollute the water courses; this is popular belief throughout this section. He says:

I had no cases in 1904, but 2 well-marked cases last year (1903). The first was an old man, a sheep herder, from the Quinn River country. My second case was a school-girl, age 18, who had attended a school picnic in Cross Canyon, about 7 miles from town. I questioned her closely as to the possibility of a tick bite, but she said that she did not remember having any ticks on her for months past. However, a band of sheep had been driven through the upper end of the canyon the same week she attended the picnic.

Both of my cases showed marked tendency to collapse, requiring heart stimulants all the time. Outside of that the treatment consisted of maintaining the body temperature and a careful attention to the diet.

I have been informed by the people who have had the disease, and who have seen numerous cases, that if the patient gets chilled the results are fatal, and my experience with the girl mentioned above makes me think there is something in that point. She got the covers off one night, and I spent several hours with her before her condition became satisfactory again.

I think there has been a marked diminution in the number of cases noted in this locality in the last five or six years.

*Oregon.*—According to Anderson (1903c, p. 8), the mild form of the disease has been reported in eastern Oregon, but he does not state where and by whom it was observed.

*Utah.*—Sweet (1896) states that the disease does not to his knowledge occur in Utah, but Smith (1905) (see below, p. 116) reports a possible case.

*Alaska.*—McCullough (1902, p. 225) says that reports show that the same disease occurs in Alaska, and Gwinn (1902) says that he has repeatedly read newspaper accounts of a disease about Klondike which very much resembled "spotted fever."

#### COMPARISON WITH THE OTHER DISEASES.

*Bovine piroplasmosis* occurs in the United States, West Indies, Argentine, Southern Venezuela, Uruguay, and apparently Brazil; in Australia, Africa (Algiers, Egypt, Uganda, Kamerun, Cape Colony, German East Africa, etc.); in southwest Russia, Bulgaria, Hungary, Roumania, Turkey, Italy, France, Germany, Finland, Norway, and perhaps in Great Britain (Nuttall, 1904, p. 220). Texas fever may extend from 37° to 38° north latitude to the Gulf of Mexico (for exact area, see maps published by the United States Bureau of Animal Industry). Hemoglobinuria is found in certain swampy regions on the Danube.

*Ovine piroplasmosis* is reported from Roumania, Italy, Turkey, France, and a similar affection occurs in St. Thomas, West Indies, and in South Africa. Johnson reports piroplasmatic ictero-hematuria for Deer Lodge, Mont. According to Babes, the cases on the lower Danube occur in marshy regions.



*Equine piroplasmosis* has been observed in South Africa and Germany, and perhaps in Venezuela.

*Canine piroplasmosis* is reported for Italy, France, and South Africa. Piana and Galli-Valerio (1895) noticed it in dogs which had hunted in marshy localities. Hutcheon (1893, p. 477) states that in South Africa it is very common in coast towns and districts, but comparatively rare in higher inland districts of Cape Colony; nevertheless, it prevailed about Herschel in 1893.

From these data it will be observed that piroplasmatic diseases have a wide geographic distribution, but are not confined chiefly to foothills of mountain ranges; they may be found in swampy valleys.

The question of distribution probably depends more upon the ability of the transmitting tick to develop than upon any other one factor, and as ticks develop in the region of "spotted fever," a comparison of the geographic distribution of the various diseases gives us but meager details upon which to form any judgment regarding the question now at issue.

#### NUMBER OF CASES.

*Montana.*—Gwinn (1902) estimates the number of cases he has seen in fifteen years as about 200. Wilson and Chowning (1902a, p. 132; 1903a, p. 28; 1904a, p. 33) think that probably 200 cases of the severe type have occurred (in the Bitter Root Valley) since the disease first appeared; they collate 114 cases (1903a, pp. 32-41) since 1885 which they collected from correspondence with the physicians of the valley, but they give cases 11, 18, 19, 37, 40, 108, 113, and 114 as doubtful. Anderson (1903c, pp. 12-18) increased this compilation to 121 cases.

Taking the cases given in the tables published by Wilson and Chowning and Anderson for the Bitter Root Valley we find the following distribution by years from 1885 to 1892, inclusive:

Year.	Cases.	Deaths.	Per-centage deaths.	Year.	Cases.	Deaths.	Per-centage deaths.
1885 .....	1	1	100.0	1896 .....	6	6	100.0
1886 .....	1	1	100.0	1897 .....	6	5	83.3
1887 .....	.....	.....	.....	1898 .....	3	2	66.6
1888 .....	3	1	33.3	1899 .....	23	14	60.8
1889 .....	3	3	100.0	1900 .....	12	9	75.0
1890 .....	1	1	100.0	1901 .....	14	10	71.4
1891 .....	6	4	66.6	1902 .....	21	15	71.4
1892 .....	3	1	33.3	Date? .....	4	2	50.0
1893 .....	4	2	50.0	Total .....	114	80	70.17
1894 .....	.....	.....	.....				
1895 .....	3	3	100.0				

As these statistics are based upon notes which the local physicians wrote up largely from memory, it is perhaps an open question whether we should draw the conclusion that the disease has increased in frequency since 1898, as the number of inhabitants in the valley have increased, or whether we should attribute the fewer number of cases reported for earlier years to the fact that the earlier cases had passed out of the memory of the local physicians.

Anderson (1903c, pp. 4, 16-19) reports but 9 cases for 1903, with 3 deaths, but he speaks (1903a, p. 40) of 10 cases under treatment.

Wilson and Chowning (1904a, p. 32) refer to having seen 10 cases personally in 1903, and to having collected data from 2 cases which they did not see. To these 12 cases, 7 deaths, should be added the following:

1903, August-September.—R. B., telegraph operator, was at Woodman, on Lo Lo stream. Was taken sick with a chill Saturday evening (August 29), and brought to Missoula Monday morning (August 30), where he later died. He was aware of the "tick theory" which had been published, but claimed that he was not bitten by ticks. Mr. and Mrs. George Kieth say positively that there was no history of tick bite in this case. He was seen by Doctor McCullough and Dr. Parsons.

1903, August-September.—J. G. W., 24 or 25 years old; so far as he knew, he was last bitten by a tick in July. About the last of August he was taken sick and saw Doctor McGrath, who made a diagnosis of "spotted fever" and sent him to St. Patrick's Hospital in Missoula. He reached Missoula September 1 and was treated by Doctor Mills. The case, which was "typical," ended fatally on September 5.

During the season 1904 there occurred in the Bitter Root Valley 11 cases, with 9 deaths. Thus we may complete the above table (p. 29) as follows:

Date.	Cases.	Deaths.	Lethality.
			<i>Per cent.</i>
1885 to 1902.....	114	80	70.17
1903.....	14	9	64.29
1904.....	11	9	81.82
Total Bitter Root Valley, 1885 to 1904.....	139	98	70.5
Gates's cases near Bridger, 1894 to 1904.....	17	3	17.6

COMPARISON.—In *bovine piroplasmosis* large numbers of animals may be affected in the same season. In some years 20 per cent of the sheep in the swampy islands of the lower Danube are destroyed by *carceag*.

The occurrence of a large number of cases of a piroplasmatic infection in a given district is natural, when we consider how very prolific an animal the tick is. A female tick lays hundreds of eggs, and it is the next generation (developing from the eggs of an infected female) which carries the infection. Accordingly, for every infected female which lays eggs, there may be hundreds of infected individuals of the next generation, hence piroplasmatic diseases are apt to attack large numbers of patients at about the same time in the same locality, and if "spotted fever" is a piroplasmosis, transmitted by a tick, we should expect a large number of cases to develop in any locality in which one case develops. This, however, is exactly what we do not find in "spotted fever," and this was the first point to lead me to seriously doubt the tick hypothesis. Wilson and Chowning lay considerable stress upon the point that, according to their studies, "in no instance have two or more persons with the same food or water supply been simultaneously stricken with this disease."

#### LOCALITY OF INFECTION.

Idaho.—Several Idaho observers speak especially of the fact that the disease is found in the valleys; and Collister (1896, p. 63) says that it is rarely found in high mountains. Maxey (1899, p. 434) states that in his opinion it is contracted while

the patients are residing or sojourning in or near the foothills of the mountains; he has carefully investigated this question of residence in every case coming under his observation and has found that without exception there was a history of a longer or shorter residence, just prior to the sickness, in or near the mountains or along some mountain stream where the sole water supply came from melting snow.

*Montana.*—Gwinn (1902) says that in the Bitter Root Valley at least 90 per cent of the cases occur on the west side of the river. Wilson and Chowning (1902a, p. 132) state that in Montana the cases are confined to the eastern foothills of the Bitter Root Mountains (see also above, p. 25). They describe this range as very rugged, the top being covered with snow until about July 1, and some peaks capped throughout the year; the range on the east side of the valley is less rugged, though the snow remains almost as long in the spring as on the west side; on the foothills the snow melts from sunny exposures as early as February, the bulk of it disappearing in April and May; the climate of the valley is very mild, as is evidenced by the many orchards of apple, cherry, and plum trees; the altitude of the valley is about 3,500 feet above sea level. In their later papers (1903a, pp. 42, 67; 1904a, pp. 33, 34, 43) they practically repeat these statements, laying stress upon the localization of the Bitter Root Valley infection to the foothills on the west side. They do not discuss the topography of the Rock Creek cases.

Anderson (1903a, p. 506; 1903c, p. 8), in discussing the localization in the Bitter Root Valley, says that the disease is sharply localized on the west bank of the Bitter Root River, no case having been known on the east side of the river who had not a short time previously visited the west side. Certain places, he states, seem to be more heavily infected than others.

From the list of cases for 1904, given on page 26, it will be seen that these statements as to localization are borne out to a certain extent, but that while 6 cases occurred on the west side of the Bitter Root River, 1 case certainly occurred on the east side, and in 4 other cases no evidence was obtained that the patients had visited the west side shortly before their illness (except that one had passed through on a train).

In connection with the larger number of cases on the west side it should be mentioned that there is a marked difference in general conditions between the east and west sides. On the west side there is much more timber and underbrush; the west side is narrower than the east and is watered by more numerous mountain streams, as is shown in the map published by Wilson and Chowning (1903a) and Anderson (1903c). In driving through the valley one is struck by the difference in the general conditions of moisture (the east side being less damp) and by the generally better economic and hygienic conditions than on the west side.

In this connection, however, it is interesting to note that there is a short stretch of land, several miles in length, on the west side, between Carlton and Lo Lo, for which neither Wilson and Chowning (1903a, map) nor Anderson (1903c, map) report any cases of spotted fever for the years 1885 to 1903, inclusive. This particular locality resembles, in condition, the east side much more closely than does any other portion of the west side between Lo Lo and Hamilton. Remarking upon this point to one of the farmers in the locality in question, I was



informed by him that in said locality the people had never experienced "spotted fever" and did not fear it.

Whether or not the absence, or at least the apparent absence, of spotted fever from this restricted area between Carlton and Lo Lo is connected with the more advanced condition, as found also on the east side, is one of the points to which future investigation should be directed.

It will be noticed that while Wilson and Chowning (1902a, 1903a, 1904a) and Anderson (1903a, 1903c) speak of the east side of the Bitter Root Valley as the uninfected locality and the west side as the infected locality, other statements Wilson and Chowning make lay stress upon the fact that infection is more or less limited to the foothills on the west side. Maxey also mentions especially the foothills in Idaho.

To Ashburn and to me these references to the foothills seemed to be of no little importance, and they were rather strongly confirmed by our inquiries, for we found the general opinion to be that it was chiefly in the foothills that infection took place. This indicated that the infectious area, or at least the area of more intense infection, was bounded on the east, not by the Bitter Root River, but by the "bench," or foothills, and as a matter of fact the local physicians and inhabitants seemed quite generally to be under the impression that the narrow lowlands close to the river were comparatively, if not entirely, safe so far as infection was concerned.

COMPARISON.—As shown on page 29, this tendency to limitation of infection in the foothills of mountains does not seem to agree with piroplasmosis in cattle, sheep, and dogs.

#### SEASONAL DISTRIBUTION.

Practically all authors lay stress upon the fact that the affection under discussion is preeminently a disease of the spring months, but it might be well to direct attention to the fact that any given date (as April 15) in the localities in question does not necessarily correspond in season to the same date in localities in the Southern or Eastern States.

*Idaho.*—Bowers (1896, p. 63) says that "spotted fever" occurs only during the spring, from about the 1st of March to the middle of May. According to Collister (1896, pp. 62-63) it appears in March and continues until the latter part of June. After Fairchild (1896) it usually prevails from April 1 to July 1. Maxey (1899, p. 434) reports that it invariably occurs during the spring months. The Medical Sentinel (1899, p. 457) says that "the greater prevalence of this fever in the spring suggests that the infection enters the system more easily at this time, or that the morbid agent is to be found in greater profusion. Reasoning on grounds of analogy it would seem that the former is the more likely explanation. No doubt stockmen, herders, and others living in these high altitudes have their powers of resistance considerably lessened by the rigors of a long winter; exposure to cold and deprivation of certain articles of diet producing a condition approaching scurvy. Naturally, then, we would expect in a weakened system an exhibition of virulence from the first pathogenic



microbes to be liberated and distributed by the melting snows of the spring. There is here a resemblance to a water-borne disease, and until Widal's serum test (see below, p. 66) is tried there will be cause for skepticism and a diversity of opinion as to the true nature of the malady."

*Montana.*—McCullough (1902) says that "spotted fever" occurs in the spring, more likely in April and May than at other times, yet it has occurred as early as January and as late as July. According to Gwinn (1902) time bears a causal relation, as is shown by the fact that the disease does not occur during the latter half of the year; nearly all cases occur in the months of April, May, and June, May being the worst month. Wilson and Chowning (1902a, p. 132; 1903a, pp. 42, 68; 1904a, pp. 35, 43) state that the disease occurs only in the spring. The earliest recorded case began March 17, and the latest about July 20, though most cases occur between May 15 and June 15. There are no records of any cases occurring between August 1 and March 17, though there are rumors of some cases having occurred as early as February. Anderson (1903c, p. 8) agrees essentially with Wilson and Chowning.

Wilson and Chowning (1903a, p. 43) print a table of the cases, distributed by months; they later insert (1904a, p. 35) the cases of 1903. In the following table I add to their cases the Bitter Root Valley cases I have collected.

Month.	Reported by Wilson and Chowning. 1904a, page 35.	Additional cases.	Total.	Remarks.
January .....	.....	(?)	(?)	See McCullough, 1902; uncertain case, see Cobb, 1902, page 1868.
February .....	.....	(?)	(?)	Rumors, see Wilson and Chowning, 1902a, page 132; a few cases when March was mild, see Cobb, 1902, page 1868.
March .....	6	.....	6	
April .....	24	2	26	The 2 additional cases (1, 2) in 1904.
May .....	46	7	53	The 7 additional cases (3, 4, 5, 6, 7, 8, 9) in 1904
June .....	35	2	37	The 2 additional cases (10, 11) in 1904.
July .....	5	.....	5	
August .....	.....	} 2	2	Cases in 1903, see page 30.
September .....	.....			
"Spring" .....	10	.....	10	
Total .....	126	13	139	

Of the 17 cases reported by Gates for another locality, 4 occurred in April, 6 in May, and 7 in June.

It is a more or less popular belief among some of the inhabitants of the Bitter Root Valley that cases of "spotted fever" are more likely to occur during the time that the streams are rising than while they are falling. This would indicate that it occurred either during or following a rise in temperature, such as would melt the snow on the mountains, or during or following a rainfall.

Through the kindness of Prof. Willis Moore, Chief of the United States Weather Bureau, I have been able to obtain the daily temperatures and rainfall for Missoula for the months of February-September, inclusive, 1899-1904, inclusive, so far as these have been recorded by volunteer observers (Prof. M. J. Elrod), and I have attempted to plot the cases of "spotted fever" which are reported for the Bitter Root Valley for the corresponding days. While this study was interesting, it is not entirely satisfactory for several reasons; in the first place,

the exact date of the onset in a number of cases is not given; further, the temperature and precipitation varies some in different parts of the valley, and I could not obtain these data for the exact locality where the cases occurred. Hence the results obtained are only approximate.

I find that of the cases upon which even an approximate comparison could be made 13 cases developed in the valley within seventy-two hours following an increase in temperature at Missoula, but no precipitation was reported for Missoula; 45 additional cases developed in the valley within seventy-two hours following an increase in temperature at Missoula, and precipitation is reported for Missoula during the same period. Thus a total of 58 cases occurred during or following conditions which would result in a swelling of the streams, hence more moist general conditions. One additional case developed during a decrease of temperature at Missoula, without any contemporaneous precipitation.

Without laying too much stress upon these data, because of their incompleteness, it is rather striking that of the 59 cases in which the given data could be compared, 58 of them, or 98.3 per cent, occurred under conditions which would result in an increase in the amount of running water in the valley, thus apparently bearing out the popular view that "spotted fever" is more likely to develop during a rise rather than a fall of the valley streams.

It is also interesting to note that by far the majority of the cases occur on the west side of the river, which is more moist than the east; that the disease seems to be a disease of valleys, which are naturally more moist than are the plains. Future investigations, therefore, have the interesting problem to solve whether this concurrence of moisture with the infection is of any significance or is a mere coincidence. The relation of the moisture to the tick theory is not apparent to me.

Taking the monthly maximum temperature at Missoula in connection with 88 cases which could be plotted, it was found that the lowest maximum was 48.1° F. (2 cases), the highest, 87.6° F. (2 cases); 3 cases occurred with monthly average maximum from 48.1 to 49.6° F., 20 cases with monthly average maximum from 54.2 to 58.6° F., 34 cases with monthly average maximum from 63 to 69° F., 26 cases with monthly average maximum from 71.7 to 76.6° F., 5 cases with monthly average maximum from 80.5 to 87.6° F.

For the same 88 cases, the lowest monthly average minimum temperature at Missoula was 22.2 (1 case), and the highest average minimum, 51.2° F. (2 cases). Four cases occurred with a monthly average minimum from 22.2 to 28.5° F., 38 occurred with a monthly average minimum from 31 to 38.7° F., 44 occurred with a monthly average minimum from 41 to 48.7° F., and 2 with a monthly average minimum of 51.2° F.

For the same 88 cases the lowest difference between the monthly average maximum and minimum temperature for Missoula was  $19.6^{\circ}$  F. (2 cases), the highest  $35.8^{\circ}$  F. (2 cases); for 2 cases there was a monthly average difference of  $19.6^{\circ}$  F.; for 70 cases there was a monthly average difference from  $21.7$  to  $29.8^{\circ}$  F., inclusive; for 16 cases there was a monthly average difference from  $30.4$  to  $35.8^{\circ}$  F.

Thus a monthly average maximum of  $63$  to  $73^{\circ}$  F., inclusive, obtained in 59 out of 88 cases, or 67 per cent of the cases; a monthly average minimum of  $37$  to  $46^{\circ}$  F., inclusive, obtained in 58 out of 88 cases, or 65.8 per cent of the cases; of 88 cases 70 cases, or 79.5 per cent, occurred during an average monthly difference of  $21.2$  to  $29.8^{\circ}$  F. between maximum and minimum temperature, and 55 of these cases, or 60.2 per cent of the 88 cases, occurred during a monthly average difference of  $25.2$  to  $29.7^{\circ}$  F., inclusive, between the monthly maximum and monthly minimum.

It would therefore appear that, so far as can be concluded from the data at our disposal, there seems to be some connection, either direct or indirect, between the temperature of the air and the development of cases, in that up to a certain point an increase in temperature is coincident with the development of cases, while beyond that point a further increase in temperature seems not to favor the appearance of new cases. Of course an increase in temperature increases the amount of water resulting from the melting snow, but there finally comes a time when the supply of snow is greatly decreased, hence a further increase in temperature would not have the same effects upon the amount of water in the valley.

Our data upon these points are not sufficiently exact to permit of positive conclusions, but such as the data are they tend to support rather than to negative the popular idea that the melting snow has some direct or indirect connection with the development of cases, or at least they tend to show that conditions which favor the melting of the snow also favor the appearance of cases of spotted fever.

Taking the amount of precipitation, including rain, hail, sleet, and melted snow (not from the mountains), we find that 14 cases occurred in six months showing a total monthly precipitation of 0.37 to 0.68; 50 cases occurred in eleven months showing a total monthly precipitation from 1.02 to 1.98; 3 cases occurred in one month showing a precipitation of 2.78; 7 in a month showing precipitation of 3.84, and 14 in 2 months showing precipitation of 4.19 and 4.53.

The lowest precipitation in any month during which a case developed was 0.37 (1 case); the highest number of cases in reference to precipitation were as follows: 6 cases, 0.65; 9 cases, 1.2; 9 cases, 1.44; 15 cases, 1.28; 7 cases, 3.84; 6 cases, 4.19; 8 cases, 4.53.

From this it is seen that in general fewer cases have developed during the epidemic months with a precipitation under 1 than with



a greater precipitation, and while the greatest number (15) developed with a precipitation of 1.28, the average stands as follows: 2.33 cases between 0.37 and 0.68; 4.5 cases between 1.02 and 1.98; 3 cases at 2.78; 7 cases at 3.84; 7 cases between 4.19 and 4.53.

While these data are too incomplete to permit of definite conclusions, still, such as they are, they are in harmony with the view that cases are more likely to occur coincident with a rising of the streams than with their fall.

COMPARISON.—Texas fever, in the United States, occurs in summer and fall; hemoglobinuria in the Danube region occurs usually in the late spring, summer, and late fall. Carceag is reported for the Danube region, especially in May and June. Canine piroplasmiasis prevails at the Cape chiefly in summer and autumn, and is reported in Europe for April, September, and October.

We should not be led astray by this comparison of months. The life history and seasonal occurrence of ticks in different places might vary according to the species of tick involved and according to the climate.

#### AGE AND SEX OF PATIENTS.

*Idaho*.—Fairchild (1896) says that all classes and all ages are affected, the rich, the poor, the weak, the robust, the young, the old, males and females, alike. Bowers (1896) agrees that the disease attacks persons in all conditions of life, but males in larger proportion. According to Dubois (1896, p. 64) "spotted fever" attacks persons of all ages, but adults of both sexes are more subject to infection than are children. According to Maxey (1899, p. 434) it is much more frequent in men on account of their exposed occupations, and this will explain also why children are rarely, if ever, affected; the youngest case he knows of was in a patient 6 years old, the oldest in a patient nearly 70 years of age.

*Montana*.—Gwinn (1902) reports that in his observations he has noted that age, sex, and amount of vitality play little or no rôle in infection.

The first actual statistics concerning age and sex were collected by Wilson and Chowning (1903a, p. 43), based upon 114 cases; they conclude (1903a, p. 68; 1904a, p. 43) that the disease attacks alike patients of any age or either sex, though those whose occupations or pleasures take them to the foothills of mountains in the spring-time are most affected; they report one case (1903a, pp. 38, 59) in a child 2 years old and another (p. 32) in a babe 2 days old; they give a very interesting table of 114 cases, and conclude that the cases are too few to warrant elaborate conclusions, but that it is probable that the large number of cases occurring in males (36) of 20 to 40 years, and in females (25) of somewhat younger age (10 to 40), is due to the increased exposure to infection through occupation or pleasure taking them outdoors in the foothills and mountains in the spring of the year.

Anderson (1903c, p. 9) shows that of 121 cases 76 were males and 45 females, the difference in number in the two sexes being probably due to a greater liability to exposure on the part of men on account of occupation. He gives the ages of 15 to 50 as being most liable to infection, and reports 18 months as the youngest and 74 years as the oldest cases recorded.

The Wilson and Chowning table (1903a, p. 43) of 114 cases was increased by them (1904a, p. 36) to 126 cases. It is here increased to 139 cases, to contain the Bitter Root Valley patients observed in August–September, 1903, and in the 1904 outbreak.



The number of cases for Bridger and vicinity is not sufficiently large to permit of comparison by age, but it may be noted that 12 were in males and 5 in females.

Age, years.	Males.						Females.						Both sexes.				
	Compiled by Wilson and Chowning, 1904a, p. 36.		Additional.		Total.		Compiled by Wilson and Chowning, 1904a, p. 36.		Additional.		Total.		Total.				
	Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.		Cases.	Deaths.	Cases.	Deaths.	Cases.	Deaths.		Cases.	Number.	Per cent.
						Number.	Per cent.						Number.	Per cent.			
Inclusive under 5...	8	4	---	---	8	4	50.0	5	5	1	1	6	6	100.0	14	10	71.4
6 to 10.....	6	5	1	0	7	5	71.4	7	4	---	---	7	4	57.1	14	9	64.2
11 to 20.....	8	5	2	2	10	7	70.0	11	5	---	---	11	5	45.4	21	12	57.1
21 to 30.....	17	13	2	2	19	15	78.9	7	3	3	3	10	6	60.0	29	21	72.4
31 to 40.....	24	19	1	1	25	20	80.0	11	7	---	---	11	7	63.6	36	27	75.0
41 to 50.....	8	6	---	---	8	6	75.0	2	1	---	---	2	1	50.0	10	7	70.0
51 to 60.....	3	2	---	---	3	2	66.6	2	1	---	---	2	1	50.0	5	3	60.0
61 to 80.....	4	4	1	1	5	5	100.0	2	2	---	---	2	2	100.0	7	7	100.0
Not stated.....	1	1	a1	1	2	2	100.0	---	0	b1	0	1	0	0	3	2	66.6
Total.....	79	59	8	7	87	66	75.9	47	28	5	4	52	32	61.5	139	98	70.5

<sup>a</sup> Baskerville, 1903.

<sup>b</sup> Merrick's case, 1903.

This table, October 31, includes 11 additional cases for Bitter Root Valley, 1904.

So far as can be judged from these statistics, the lethality of this disease for the Bitter Root Valley has been as follows:

Average of all cases, 70.5 per cent.

Average of all males, 75.9 per cent.

Average of all females, 61.5 per cent.

For females from 11 to 20 years, 45.4 per cent.

For males under 5 years, females 41 to 50 years, and 51 to 60 years, 50 per cent.

For females from 6 to 10 years, and all cases from 11 to 20 years, 57.1 per cent.

For females from 21 to 30 years, and all cases 51 to 60 years, 60 per cent.

For females from 31 to 40 years, 63.6 per cent.

For all cases from 6 to 10 years, 64.2 per cent.

For males from 51 to 60 years, 66.6 per cent.

For males from 11 to 20 years, and all cases from 41 to 50 years, 70 per cent.

For all cases from 21 to 30 years, 72.4 per cent.

For males from 41 to 50 years, and all cases 31 to 40 years, 75 per cent.

For all males, average, 75.7 per cent.

For males from 21 to 30 years, 78.9 per cent.

For males from 31 to 40 years, 80 per cent.

For males from 61 to 80 years, females 61 to 80 years, all cases 61 to 80 years, and females under 5 years, 100 per cent.

COMPARISON.—In Texas fever, the disease attacks both sexes, but seems to be more seldom in calves than in adults; Starovici says that cows are rarely attacked with hemoglobinuria, and that the disease is unknown in calves; also that only adult sheep are affected with carceag. According to Robertson (1901, p. 327), canine piroplasmiasis attacks both young and old dogs; Nocard and Motas (1902, p. 275) found young dogs to be much more susceptible than adults.

## OCCUPATION OF PATIENT.

*Idaho*.—"Spotted fever" is mostly confined to teamsters, who camp out during the summer months (Figgins, 1896, p. 64). Stockmen in general, but particularly sheep men, prospectors, and miners, are special prey of this disease, as their occupations take them into the mountains. These men are exposed to all kinds of weather day and night, sleep on damp ground, in damp beds, their meals are irregular, their food is coarse and poorly cooked, and proper personal cleanliness seems to be out of the question (Maxey, 1899, p. 434). Spotted fever occurs among stockmen, miners, and other mountaineers (Medical Sentinel, 1899, p. 456).

*Montana*.—Anderson (1903c, p. 8) states that all occupations that cause the person to be exposed to the bite of ticks, such as stockmen, and especially sheep herders, miners, prospectors, lumbermen, ranchmen, and those whose duties take them into the brush, are subject to the disease.

Wilson and Chowning (1902a, p. 132; 1903a, p. 42; 1904a, pp. 34-35) state that the population of the Bitter Root Valley is made up largely of fairly well-to-do ranchers, the majority of whom have come from Missouri, Georgia, and the Carolinas. They are, as a rule, cleanly and healthy. The lumber industry is an important one, and many cases of spotted fever have arisen about sawmills and on ground recently cleared of timber.

Taking the occupations as given by Wilson and Chowning for cases 1 to 121, and adding others reported by Anderson (1903c) and those collected for the Bitter Root Valley by Ashburn and myself, we have the following data:

Thirty-eight patients were children, or boys and girls, as follows: 4 schoolboys, 4 schoolgirls; 30 children, occupation not given, but probably most of them lived on farms.

Twenty-six patients were housewives or housekeepers, probably the majority on farms.

Twenty patients were connected with farms, as follows: 19 farmers or ranchmen, 1 farmer's daughter.

Sixteen patients were connected with the lumber industry, as follows: 10 lumbermen, 2 lumber jacks, 1 lumber cruiser, 1 sawmill man, 1 business man, who had been at a sawmill.

Eleven patients are listed as laborers, but the kind of labor is not stated.

Eleven patients are not listed relative to their occupation. Two patients are listed as trappers; 2 patients are listed as prospectors; 4 patients are listed (1 each) as stonemason, teamster, miner, and telegraph operator (who was in the valley on other work at the time.)

Two female patients are listed (1 each) as nurse and school-teacher.

In this list it is striking that a very large number of the patients were either on farms or connected with the lumber industry, but it should be remembered that farming and lumbering are the chief occupations in the valley; hence, other things being equal, these occupations would be expected to furnish a large percentage of the patients.

In Gates's statistics the following occupations are given:

Four children (2 boys, 2 girls), 1 housewife, 6 ranchmen, 1 sheep herder, 1 stockman, 1 trapper, 1 freighter, 1 nurse.

## TYPES OF CASES.

*Idaho.*—The type of the disease which appears in Idaho, as described by Doctor Maxey, is apparently very much milder than that of the severe form appearing in Montana, though all cases show the peculiar eruption. (Wilson and Chowning, 1902a, p. 132; 1903a, p. 44; 1904a, p. 37.)

*Montana.*—Gwinn (1902) divides the cases into mild, medium, and most severe.

Most physicians in the Bitter Root Valley who have had experience with the disease recognize but one type—a severe and usually fatal form—the principal diagnostic feature of which is the “spots.” Several physicians recognize a mild type in which there are no “spots.” There is much difficulty in the accurate diagnosis of the mild type and, though its existence must be recognized, yet during the investigations herewith reported all of the examinations except 1 were made on cases of the severe type. (Wilson and Chowning, 1902a, p. 132; 1903a, p. 44; 1904a, p. 36.)

Some of the physicians in the Bitter Root Valley speak of cases of “local infection” with “spotted fever.” Wilson and Chowning (1903a, p. 61) report one such case, but do not include it in their statistics. I am unable at present to admit these cases. (See Stiles, 1905, pp. 14–15).

## COMPARISON:

Smith and Kilborne (1893, p. 15) describe for Texas fever two types, an acute fatal type and a mild, rather prolonged, usually nonfatal type.

For canine piroplasmiasis, acute and chronic types are described.

## SYMPTOMATOLOGY.

The symptomatology of the disease under consideration has been discussed by Wood (1890), Maxey (1899), McCullough (1902), Gwinn (1902), Wilson and Chowning (1902, 1903, 1904), Anderson (1903), and Gates (1903). Wood and Maxey have described the symptoms as they are observed in Idaho and the other authors as they are observed in Montana. As no one has as yet brought all these observations together it may be well to do so at this time in connection with the symptoms observed in Montana in 1904.

As stated in the introduction (see above, p. 10), my trip did not contemplate a study of symptomatology, but it naturally became necessary for me to familiarize myself more or less with this phase of the subject.

The symptoms are quite well marked and very constant (Maxey, 1899, p. 435).

All symptoms and lesions indicate that the disease is due to a specific infection (Wilson and Chowning, 1903a, p. 68; 1904a, p. 43).

## PREVIOUS CONDITION OF PATIENT.

*Idaho.*—Bowers (1896, p. 63) refers to exposure to cold, drafts, and dampness as auxiliary causes.

*Montana.*—Gwinn (1902) says that at least 90 per cent of the cases give a history of having been exposed to wet or cold, or both, from one-half to three days prior to the attack; and although the exposure and constipation are so constant a feature as to be apparently operative in the cause, yet little stress can be laid upon them from the fact that they do not have such effect at other times of the year or in other localities. Wilson and Chowning (1902a, p. 132; 1903a, p. 43; 1904a, p. 35) say that

the age and sex and general health of the patient appear to have no part in determining susceptibility to the disease; a large number of cases give a history of recent exposure to wet or cold or of overexertion shortly before the attack, but in several cases all such history has been absolutely excluded; many of the patients have suffered somewhat from indigestion and constipation immediately prior to the attack, in others no such condition existed.

#### PERIOD OF INCUBATION.

*Idaho.*—The period of incubation is uncertain, probably 10 to 21 days (Bowers, 1896, p. 63).

*Montana.*—Gwinn (1902) says that in so far as exposure to wet and cold may be a cause, the onset is on an average of 18 hours after exposure. Anderson (1903a, p. 21) gives the incubation as 3 to 10 days, usually about 7. Wilson and Chowning (1904a, p. 37), arguing on the theory of transmission by ticks, state that though all cases occurring in 1902 and 1903 gave a history of tick bites (see, however, p. 30) shortly before the onset of the symptoms, only the following cases gave a clear history of a definite incubation period:

	Days.
Cases 94, 97, 117, 124, 125 .....	2
Case 96 .....	3
Case 119 .....	5
Case 116 .....	6
Case 112 .....	7
Case 115 .....	8
Cases 120, 121 .....	2 to 5

Several of the cases which occurred in 1904 give points of comparison upon the period of incubation.

Arguing on the tick hypothesis, it may be noted that:

1904, case 2 was bitten by ticks April 24, and fever was noticed the following day.

1904, case 8 was bitten by ticks May 15, and was taken sick the following day.

1904, Gates's case 15 started for Clarke Fork Canyon May 29, remaining in that vicinity about 4 days, during which time he was bitten by ticks in five or six places; he showed first symptoms 7 days after first tick bite.

1904, Gates's case 16 showed symptoms 5 days after tick bite.

Not arguing on the tick hypothesis, it may be noted that—

1904, case 3 moved in January to house in which she was taken sick on May 3, making a maximum of about 4 months in the infected locality before she became ill.

1904, case 10 left Iowa 6 weeks prior to onset, 5 of these 6 weeks being spent in Bozeman, Mont.; thus this patient was in Montana a maximum of 6 weeks prior to illness.

1904, case 11 had been in the United States 4 weeks, in the Bitter Root Valley 19 days, and at the house where she was taken ill 14 days prior to onset of the disease.

1904, Gates's case 15 was taken ill about 7 days after he visited the locality in which infection is supposed to have taken place; and

1904, Gates's case 16 was taken ill 6 days after sleeping with a case (15) in its initial stage.

These data would indicate that either upon basis of the tick hypothesis or upon basis of infection by some other unknown method, the disease may develop within 6 days after exposure; the maximum



and minimum time between exposure and onset can not be well established from the data now at our disposal.

Arguing upon the tick hypothesis it would seem that the disease might develop within a day after exposure.

COMPARISON.—Smith and Kilborne (1893, p. 15) point out that the term "period of incubation" is used in two different senses in connection with Texas fever. In experimental cases of Texas fever it is 6 to 10 days after the cattle are inoculated with Texas fever blood, the time depending on the number of parasites originally introduced, the predisposition and age of the animals, and the season of the year. Starcovici gives about 14 days as incubation period for hemoglobinuria, and "about 8 days (?)" for carceag. For canine piroplasmosis the period is given as 10 days from the date of visiting a tick belt (Robertson); Nuttall found it to be 13 to 21 days in dogs bitten experimentally by ticks; upon subcutaneous injection the period varies from 3 to 10 days.

#### ONSET.

*Idaho.*—During incubation there is a slight headache and a feeling of lassitude and inaptitude for work; during the first week following this period the patient complains of chilly feelings, nausea, loss of appetite, intense headache, pain in the back and legs, a muscular soreness and stiffness of the entire body, and he takes to bed with a temperature of 102° to 105° F., pulse 90 to 120 (Bowers, 1896, p. 63). According to Collister (1896, p. 63) many cases are taken suddenly without previous malaise, some with a severe chill and others with more or less chilly shudderings frequently referred to the spinal regions; still others have little or no chill. Dubois (1896, p. 64) says that there is usually no prodromal stage and a patient is stricken down without warning with severe frontal headache, photophobia, nausea, lassitude, persistent anorexia, and intensely severe pains in joints and muscles. According to Fairchild (1896, p. 62) the attack is sometimes ushered in by a chill, but usually by two or three days of malaise, with severe headache, particularly in the back part; also shooting pains throughout the body and limbs, usually more severe in the bowels and back; the pain is neuralgic in type. Figgins (1896, p. 64) states that the disease begins with a chill, pains in the extremities, muscular soreness, and fever, the temperature ranging from 100° to 105° F., pulse 100 to 120. Springer (1896, p. 61) says there is a feeling of malaise for a few days, followed by a chill; the fever then sets in, ranging from 103° to 105° F. According to Sweet (1896, p. 61) the onset is usually accompanied by severe break-bone pains. According to Zipf (1896, p. 65) the onset is sudden, with high fever, violent headache, coated tongue, back-ache, and flushed face. Maxey (1899, p. 435) states that the patient first notices a general malaise, loss of appetite, and flashes of heat and cold, but no marked chill; the bones and muscles soon begin to ache, and by the second day the patient feels sick enough to take to his bed; he already feels very weak and depressed, and pains in the back, in the joints and muscles of the extremities, and in the head become quite severe; the bowels are constipated.

*Montana.*—In a few cases the disease seems to be preceded by a prodromal period of malaise for a few days; the attack comes on by either a well-marked chill or chilliness, simultaneous with fever, general aching and soreness of the entire body, and a flushed dusky red color of the skin. The chilliness, although most severe at the onset, often continues more or less throughout the attack, coming on at intervals—generally mornings—and becoming lighter day after day until within a week or so the chills seem but little more than chilliness from light covering (Gwinn, 1902).

According to McCullough (1902, p. 226), the onset may be marked by a sudden and severe chill and dizziness, with high fever following, associated with intense soreness seemingly of the entire muscles of the body, or it may come on insidiously,

a feeling of malaise for a few days, gradually growing worse and merging into a well-defined "bone ache" and slight chilly sensations, mostly in the morning.

Wilson and Chowning (1902a, p. 132) say that many of the cases are preceded by a short period of malaise; this is followed by a marked chill, which is usually most severe at the beginning of the attack and recurs at irregular intervals, though with decreasing severity; at the onset there is a severe aching in the bones and muscles, with pain in the back and joints; the patient is usually very weak and the headache may be severe; constipation at this period is usually present; there is considerable restlessness; a bronchial cough is frequently present; the urine is small in amount and highly colored; albumen is sometimes present; the skin is dry and the tongue, even at the onset, is thickly coated; the coat at first is white, but it becomes brownish as the fever increases, while the tongue becomes dry and cracked; sordes appear early, and may be quite pronounced; indeed, the whole facies in these respects is like typhoid. Wilson and Chowning (1904a, p. 37) also report that cases Nos. 94, 96, 97, 115, 116, 117, 119, and 120 gave a history of soreness about the tick bite and pains radiating therefrom which continued until the initial chill.

According to Anderson (1903a, p. 50; 1903c, p. 21), the patient may have chilly sensations, malaise, and nausea for a few days, then there is a distinct chill, and the person takes to bed; there is some pain in the back and head, soreness of the muscles and bones, causing a sensation as if the limbs were in a vise; bowels constipated; tongue with heavy white coat, red edge and tip; conjunctivæ congested, becoming yellowish; urine usually small in amount, with albumen and a few casts; slight bronchitis after a few days; nose bleed, sometimes quite severe, is always present. In case 74 (1903a, p. 15) the symptoms were about three days in reaching their height.

COMPARISON.—In Texas fever the fever usually precedes the outward symptoms by several days; pulse and respiration rise with the temperature; loss of appetite always, and cessation of rumination usually accompany the high fever after the third or fourth day.

Hemoglobinuria begins with exhaustion, loss of appetite, and fever; carceag with chill, exhaustion, and fever. Canine piroplasmiasis is ushered in by a fever and loss of appetite, followed by increasing prostration, ending in complete helplessness.

#### DURATION.

*Idaho*.—The period of incubation is uncertain, probably 10 to 21 days; from the appearance of prodromal symptoms until convalescence, 12 to 20 days; average period of convalescence, 1 month, very infrequently several months; in 1 case, 2 years elapsed before sunlight was borne without intense cephalalgia (Bowers, 1896, p. 63). According to Figgins (1896, p. 64) the duration is 14 to 42 days, the eruption showing for 4 or 5 months after the patient is up and around, especially when subject to heat or physical exercise. Fairchild (1896, p. 62) gives the duration as 14 to 28 days. Springer (1896, p. 61) reports duration as 2 to 3 weeks. Sweet (1896, p. 61) states that the duration is 3 weeks to 3 or 4 months, i. e., although the fever may not last longer than 21 days, the lesions may continue for months. The disease usually terminates in course of 2 or 3 weeks by lysis, usually in recovery (Medical Sentinel, 1899, p. 457).

*Montana*.—Gwinn (1902) reports that one case persisted 3 months before recovery.

Gates (1905) reports convalescence in 14 of his 17 cases as follows: In a few days, 1 case; 10 days, 1 case; 12 days, 2 cases; 14 days, 1 case; 15 days, 1 case; 18 days, 1 case; 20 days, 1 case; 21 days, 1 case; 22 days, 2 cases; about 25 days, 1 case; 28 days, 1 case; not given, 1 case.

See also Deaths, page 89.

In the 2 Bitter Root Valley recovery cases of 1904 1 (No. 4) was

taken sick about May 8 and was able to sit up May 21, thus giving a duration of 13 days from onset to convalescence; 1 (No. 10) noticed first symptoms June 2 and was discharged from the hospital June 17, giving a duration of 15 days.

COMPARISON.—Extremely acute cases of canine piroplasmiasis may last only 24 hours, but it appears more often to last 3 to 6 days; subacute cases last about 10 days; chronic cases, 21 to 62 days. Starcovici states that in hemoglobinuria the fever lasts about 5 days. In Texas fever the continuous high temperature rarely lasts longer than 8 to 10 days.

#### EPIDEMIC CHARACTER.

Under the heading "Seasonal distribution" (p. 32) it is shown that spotted fever occurs chiefly during the spring months and in certain localities, and on page 44 it is shown that all authors agree that it is not contagious. The question naturally arises as to the distribution of cases by families.

*Idaho*.—Bowers (1896, p. 63) states that spotted fever occurs sporadically. Figins (1896, p. 64) says that he has seen it in families who used water from springs and where the entire family had the disease. In the experience of Fairchild (1896) the cases have been sporadic, and it is exceptional to find more than 1 or 2 cases in the same house. Sweet (1896), however, says that frequently several cases occur in a household, again only a single case. This latter fact is often due to the patient's returning home ill after sojourning in another place up to the malaise.

*Montana*.—It is common for quite a number of the patients to come down with the disease near the same time; then perhaps there will be a respite for a week or ten days, when there will be a number of other almost simultaneous attacks in the neighborhood. If upon further investigation this proves true it may be significant in detecting the cause. (Gwinn, 1902.)

According to Wilson and Chowning (1903a, p. 68; 1904a, p. 43), in no instance have two or more persons with the same food or water supply been simultaneously stricken with the disease.

In no instance which Ashburn and I saw personally was there more than one patient in the same house, but the following cases are interesting, and possibly important, in this connection:

Cases 45 and 46 (Doctor Gwinn's patients in 1899) were two children, 3 and 5 years old, respectively (Wilson and Chowning, 1903a, p. 34). Gwinn writes me that he believes some confusion has arisen in connection with the dates of these two cases.

Cases 113 and 114 (Doctor Heine's patients at Butte in 1893) were husband and wife (Anderson, 1903c, p. 16). They were living together, and one was taken sick ten days later than the other.

In 1903 there occurred 3 cases (father and two sons) of illness in the family of A. M., on Lo Lo Creek. None of these cases is reported either by Wilson and Chowning or by Anderson:

One boy was sick with a disease which his mother supposed was "spotted fever." His father went to town to obtain medicine for the boy, and encountering a storm he became thoroughly "wet through." The father was then taken sick and was seen at the hotel in Missoula by Doctors Gwinn and Wilson. Doctor Gwinn informs me



that the father's case was one of spotted fever. A second son was also taken sick, according to his mother, also with "spotted fever." In case these patients all had "spotted fever," we here have an instance in which 3 cases occurred in one and the same family during the same spring, all the patients living in the same room in a cabin and at least two of the patients being sick at the same time. It must, however, be recalled that although I have the mother's statement to the effect that all three had "spotted fever," and although this diagnosis is accepted as correct by the neighbors, we have a physician's opinion in regard to only one of the cases.

Not far from the farm on which these cases occurred is the house in which (1904) case 5 occurred. Ashburn and I visited this house and obtained the information that at least one other case of "spotted fever," and possibly still a third case, had occurred in this same house, but the 3 cases were not simultaneous, and only 1 of them occurred in 1904.

On page 23 (see above) mention is made of a husband and wife who both had spotted fever at the same time (1900) in Boise. Doctor Bradbury writes me that the wife was taken ill at 10 a. m. and the husband was taken ill at 5 p. m., the same day.

Gates (1905, p. 112) reports two cases (15 and 16) in husband and wife, in 1904; the wife was taken ill about 6 days later than the husband.

COMPARISON.—Texas fever appears suddenly and, as a rule, at about the same time in all animals of a herd which have been exposed to the same infection together. In hemoglobinuria all of the cases of disease last in a given place scarcely longer than 14 days, then the outbreak disappears.

#### IS "SPOTTED FEVER" CONTAGIOUS?

*Idaho.*—The disease is not contagious (Bowers, 1896, p. 62; Sweet, 1896; Maxey, 1899, p. 433; Medical Sentinel, 1899, p. 457).

*Montana.*—Authors writing for Montana admit that there is no evidence that the disease is contagious (McCullough, 1902, p. 225; Gwinn, 1902; Wilson and Chowning, 1902a, 1903a, 1904a; Anderson, 1903a, c). Wilson and Chowning (1903a, p. 68; 1904a, p. 43) state that there is not even a suspicion [see, however, above, p. 23] of its ever having been transferred directly from one human being to another, except in one instance, in which an infant (case No. 17), born while the mother was suffering from the disease, developed marked purpura on the second day after birth. This child (case No. 17) was born 4 days before the death of the mother; early on the second morning after birth the physician's (Doctor Coughenour) attention was called to the child's fever and jaundiced appearance; the babe had but few spots and began to recover on the ninth or tenth day of his sickness (Wilson and Chowning, 1903a, p. 33; Anderson, 1903c, p. 13).

Regarding the noncontagious character of "spotted fever," all information which Ashburn and I obtained in the Bitter Root Valley, as well as our own personal experience, are in accord with the generally accepted view. See, however, the discussion on page 23, which seems to open up the question as to whether the malady is not contagious under some circumstances.

COMPARISON.—None of the known piroplasmatic diseases are directly contagious, but they must first pass through a tick, between two successive patients.



## POSITION IN BED.

Owing to the muscular and articular soreness, the patients lie in a position of general flexion for hours without moving (Bowers, 1896, p. 64).

See also Restlessness, page 75.

## ODOR.

There is a peculiar urinous odor to many of the patients, even when the greatest care and cleanliness are exercised in nursing them. This odor was especially marked in 1904 in cases 2, 3, 7, and 11.

In case 12, upon removing the clothing, the odor of the body led the physician to ask the patient whether he had ever had measles, to which he replied in the affirmative.

## SKIN.

## GENERAL CONDITION.

*Idaho*.—During the first week the skin is usually dry, later it is somewhat moist, and night sweats are common during the third week (Bowers, 1896, p. 63). Collister states that the skin shows no abnormal appearances. According to Figgins (1896, p. 64) it is swollen and sensitive to the touch. Maxey (1899, p. 435) describes the skin as dry and harsh.

*Montana*.—Gwinn (1902) speaks of the flushed, dusky-red color of the skin; if it is pressed while in a congested condition, it appears blanched upon removal of the fingers and is much slower in regaining its color than in health; this fact being true, in spite of the strong pulse, leads Gwinn to believe that the blood current is obstructed in the capillaries, and this belief is supported also by the nature of the eruption, the oft-occurring gangrene, and the really thick unoxygenated blood; whether this obstruction be due to changes or to alteration in the blood is hard to determine, but Gwinn inclines to the latter explanation; in addition to the eruption, the skin takes on a congested, jaundiced color; the congested and cyanotic condition of the skin causes a bloated, stupid expression of the face in most cases, which is a very diagnostic symptom. Gwinn also states that at the beginning of the second week there may be noticed a glazed appearance of the skin which, upon close examination, is found to be due to epithelium coating; it begins to scale up and shed off at the beginning of the third week.

Wilson and Chowning (1902a, p. 132; 1903a, p. 62; 1904a, p. 37) describe the skin as dry; there is a peculiar ashy paleness present, more readily observed in children and women, a few days before death (1902a, p. 132; 1903a, p. 63; 1904a, p. 38); about the second week, ordinarily, the skin presents a *glazed appearance*.

Anderson (1903a, p. 33) speaks of the lividity on dependent portions of skin and thighs (case 120); he also refers (1903c, p. 38) to a marbled appearance of the skin.

Gates (1903, p. 48) reports hot and dry skin in one case; he later (1905, p. 111) reports the skin as very dry in an additional case (1903, case 11).

## SPOTS.

## LOCATION.

*IDAHO*.—The spots first appear about the ankles and wrists, and by the end of the first week they have extended over the entire body. (Bowers, 1896, p. 63.) According to Collister (1896, p. 63) they first appear on the feet and from there spread over the body. Dubois (1896, p. 64) states that they first appear on the palms of the hands and extend from there over the body. Fairchild (1896) reports that they first are seen on the legs and arms, and soon cover the whole body. Fairchild (1896) says

that the eruption, in many cases, invades the eyes, making them very sensitive to light. According to Figgins (1896, p. 64) the spots first affect the face and hands, then the trunk, and, finally, the extremities. Maxey (1899, p. 436) states that the eruption first shows itself on the wrists and ankles, next on the forehead and chest, and in 24 to 36 hours spreads over the entire surface of the body; even the palms of the hands, soles of the feet, and the scalp are spotted.

*MONTANA.*—The spots are first discernible on the back, requiring about 24 hours to appear over the remainder of the body. (Gwinn, 1892.) McCullough says that they first appear more frequently upon the back, or simultaneously with ankles or wrists, and extend over the entire body.

According to Wilson and Chowning (1902a, p. 132; 1903a, p. 62; 1904a, p. 38) the eruption appears first about the wrist and ankles or back. It then extends over the entire body, the abdomen usually being last involved. Sometimes it spreads very rapidly, the entire surface being covered in 12 hours, but more usually one or two days pass before it reaches the maximum. The scalp, palms of the hands, and soles of the feet are frequently covered with the rash. Occasionally, though perhaps rarely, purplish spots are found on the mucous membrane of the inside of the cheeks.

Anderson (1903c, pp. 22, 38, 39) states that the spots appear first on the wrists and ankles, then on the arms, legs, forehead, back, chest, and, last and least, on the abdomen. They are never abundant on the abdomen, but other portions of the body are in some cases literally covered by the eruption. They are most abundant on the wrists, ankles, arms, and back (post-mortem). The abundance of the spots apparently bears no relation to the severity of the attack.

Gates (1903, p. 49) records a case where the spots first appeared on the buttocks, back, and thighs; the face was only slightly affected; and another case in which the spots appeared on the forehead, back of hands, wrists, and ankles. Later he (1905, p. 111) reports for his case 11 that the spots first appeared on the palms of the hands and on the feet, and they invaded the scalp in this case. In case 15 the spots appeared first on feet and hands. In case 16 they appeared first on feet, ankles, hands, and wrists.

#### TIME OF APPEARANCE.

*Idaho.*—The eruption appears during the first week about the fourth or fifth day of the attack (Bowers, 1896, p. 65) and matures during the second week. According to Dubois (1896, p. 64) it appears early, within 48 to 72 hours. Fairchild (1896) reports its appearance about the third or fourth day; Figgins (1896, p. 64) from the third to the fifth day; Springer (1896, p. 61) from the second to the fifth day; Sweet (1896) says the eruption appears within 1 to 3 days; Maxey (1899, p. 436) says the spots appear on the third to the seventh day of the fever.

*Montana.*—The spots usually appear about 3 days after the beginning of the sickness, but a few cases show no eruption until late, or a few hours before death (Gwinn, 1902). According to McCullough (1902, p. 226) they usually appear upon the third to the sixth day. Wilson and Chowning (1902a, p. 132; 1903a, p. 62; 1904a, p. 37-38) give more exact statistics on this subject; in their last summary (1904a) they say that the eruption usually begins from the second to the fifth day after the chill; in 126 cases collated, the eruption appeared on the second day in 11 cases, on the third in 65, on the fourth in 22, on the fifth in 7, on the sixth in 3, on the seventh in 2, on the eighth in 2 (both doubtful), on the ninth in 2, and on unknown dates in 12 cases. Anderson (1903a, p. 507; 1903c, p. 22) says that the spots usually appear on the third day.

Gates (1905, p. 114) reports the eruption as appearing on the second or third day in 1 case, third day in 1 case, third or fourth day in 1 case, fourth day in 5 cases, fifth day in 3 cases, sixth day in 1 case; no record in 5 cases.

In the Bitter Root Valley cases of 1904 the spots were first noticed 2 days after the first chill in 1 case, 2 days after initial fever in 1 case, third day after first chill in 1 case, fourth day after chill in 3 cases, fourth day after initial symptoms in 1 case, record incomplete in remaining cases.

## DURATION.

*Idaho.*—Bowers (1896) says that the spots reach the stage of absorption and desquamation in 8 to 21 days. They disappear slowly during the period of absorption, which is very variable—a few weeks to several months. After Collister (1896, p. 63), they can be seen for weeks, sometimes for months, after recovery, especially if the patient becomes a little chilly. Dubois (1896, p. 64) says that they fade slowly and may be discerned weeks after convalescence has set in. Fairchild (1896) reports that the eruption continues throughout the disease or until convalescence is fairly established, when it gradually fades. When exposed to cold the remains of the spots can be seen for months after complete recovery. Springer (1896, p. 61) agrees that the eruption continues throughout the attack. It is faintly visible often for many weeks, and is visible even after convalescence, especially if the surface becomes chilled; there is considerable irregularity regarding its disappearance. After Zipf (1896, p. 65), the spots stay out even after the patient feels well again. Maxey (1899, p. 436) says that as the fever declines the spots fade, but any temporary exacerbation of fever or free perspiration will freshen them temporarily, and a characteristic feature of this disease is that for several weeks after the fever has subsided the spots will show under the skin after a warm bath or active exercise.

*Montana.*—The spots fade as the fever subsides, but may not entirely disappear for weeks or months after convalescence is established (Wilson and Chowning, 1902a, p. 32; 1903a, p. 63; 1904a, p. 38). Anderson (1903a, p. 507; 1903c, p. 23) says that the spots fade as the fever declines, but show distinctly on slight return of fever or free perspiration. Warm baths produced spots 10 months after recovery.

Gates (1905, p. 115) reports that the spots were visible 4 months after recovery in his case 2 (1898), and in case 15 (1904) many spots were still visible 6 weeks after the temperature reached normal.

## CHARACTER.

*Idaho.*—According to Bowers (1896, p. 63) the spots are due to a sanguineous exudate, probably into or beneath the corium; they have a characteristic red color; on their first appearance they are one-eighth to one-fourth inch in diameter, and disappear momentarily on pressure; in 3 or 4 days they enlarge one-fourth to one-third inch in diameter, become papular, and are modified only slightly on pressure. In fatal cases they turn dark purple before death. Collister (1896, p. 63) describes the eruption as flat, rosy-red papules about one-sixth inch in diameter; when they are pressed upon, especially soon after they have formed, their color disappears, but later they do not disappear on pressure. Dubois (1896, p. 64) refers to the spots as fine, red, round papules of an erythematous nature. "The term exanthema rosalia arthrodynia more nearly expresses the disease than spotted fever." Fairchild (1896) describes the eruption as hemorrhagic in appearance; the spots vary in size from one-eighth to one-half an inch in diameter; sometimes they coalesce, covering a large surface; they do not disappear on pressure. Figgins (1896, p. 64) refers to the spots as raised, first of light-red color, assuming a dark-purple hue as the disease progresses; eruptive patches one-fourth to 1 inch in diameter, mostly of circular form. According to Springer (1896, p. 62) the eruption does not fade on pressure and in many cases there are large areas of almost black (hemorrhagic) skin, especially in



front of the tibia; the spots vary in size, averaging about one-eighth inch in diameter; they appear over the entire body, are papular, evidently extravasation of blood beneath the skin, fading to a faint blue in 4 to 30 days; they often remain for months as faint blue indurated spots on exposure to cold. According to Zipf (1896, p. 65) the spots are red in the center and blue at the margin. Maxey (1899, p. 436) states that on first appearance the spots are a bright rose color, round, unelevated, and vary in size from that of a pin head to that of a split pea; on pressure they disappear, but return quickly when released from pressure; they may or may not be tender; pathologically the eruption appears to be an extravasation of blood into the deeper layers of the skin.

*Montana.*—The eruption has the color and at a distance appears very much like measles, but it is unlike the latter in being macular; when first out the macules almost disappear on pressure; they are often situated at a hair follicle, and they vary in size—when the eruption is new, from a pin head up to a split pea; gradually the macules become darker, assuming a purple or dark-blue color, becoming harder and harder to eliminate by pressure; they increase in size so that many of them become confluent in places, producing a mottled appearance; after they become dark they have exactly the appearance of a hemorrhage under the skin; but whether or not they are a true diapedesis Gwinn (1902) is unable to say. McCullough (1902, p. 226) refers to the resemblance to a turkey egg, caused by the spots; the spots also vary and “may be seen in the form of a petechia extending to a decided ecchymosis upon an area of the body the hand would cover;” the macules partially disappear under pressure early in the eruptive stage, but later they become permanent and take on a darker hue, losing the pink tinge that predominates when the eruption first appears.

According to Wilson and Chowning (1902a, p. 132; 1903a, pp. 62-63; 1904a, p. 38) the macules are at first rose colored and consist of circular spots, varying in size from 1 to 5 mm. in diameter; they are not elevated; at first they disappear on pressure, but quickly reappear; they are sometimes tender to the touch; the appearance ordinarily rapidly changes, the macules becoming permanent, assuming a dark-blue or purplish color, and increasing in size until by confluence a mottled or marbled appearance may be given to the skin, especially on the dependent portions; in some cases the marbling covers the entire body; the color now no longer disappears on pressure; in some cases the eruption at no time becomes confluent and only small brownish or purplish petechiæ may be present, giving a speckled appearance which has been likened to that of a turkey's egg.

Anderson (1903a, p. 507; 1903c, p. 22) says that at first the spots are of a bright red color, macular at all times, from a pin point to a split pea in size; at first they disappear readily on pressure and return quickly, but if the case is a severe one they soon become darker, and in some cases are almost purple; from about the sixth to the tenth day of the disease they fail to disappear on pressure and are distinctly petechial in character; in favorable cases, about the fourteenth day they begin to lose their petechial character and disappear slowly on pressure; in some cases the eruption consists of small, brownish spots, giving a turkey egg appearance; Koplik's spots are not present (Anderson, 1903c, p. 36). Gates (1903, p. 49) in describing a case says that the petechiæ increased in size and number very rapidly during the first 2 weeks, forming large, irregularly shaped spots from the size of a little finger nail to spots one-half by one-half inch in diameter; they darkened in color, becoming bluish, with surrounding yellow tinge; they were slow in disappearing, some trace being visible 7 months after recovery.

In 1904 the skin of case 1 was mottled. In case 2 the spots were not sore to the touch. In case 3 they first appeared on the arms. In case 4 the eruption covered the legs to the knees; on the 14th it was reported as elevated and extended over trunk to face and arms. In



case 6 the spots were on the legs and trunk when patient was first seen by physician. In case 7 they were very slow and backward in appearance, in fact, and never became very pronounced. In case 8 no spots were noticed at 10 a. m. May 21 (fourth day), but at 2 p. m. they appeared quite distinct on wrist and chest; at 5 p. m. all spots disappeared; the skin then became decidedly mottled; on May 24 spots appeared in decided manner over entire back, arms, and chest. In case 9 spots were first noticed on the ankles. In case 10 first symptoms were noticed on June 2, first spots on June 6. There was profuse perspiration on May 13 in case 12, a few days after tick bite the "arm had swelled up as large as two arms and was red as a beet," the spots disappeared from the face, forehead, arms, body, and legs in the order named.

#### PATHOLOGICAL FINDINGS.

Wilson and Chowning (1904a, p. 42), reporting upon the pathological findings, say that the skin over all dependent portions of the body presented a marbled appearance; over nondependent portions it was covered with petechiæ; in all cases small wounds of the skin due to tick bites were present; the capillaries of the skin are distended with blood, which contains an excess of leukocytes; many of the red cells have escaped from the vessels into the surrounding tissues; in some cases blood-pigment granules are present in old extravasations; in a few cases phagocytes, containing infected red cells, are present, but not so many infected cells are found as are present in the spleen, kidney, and liver. Anderson (1903c, p. 38) speaks of the congested capillaries and minute extravasations in the rete extending into the stratum mucosum.

#### COMPARISON.

The spotted condition of the skin is one of the most striking clinical features of so-called "spotted fever," although it is maintained by some physicians that a mild, nonfatal type of the disease occurs in which these spots are not present.

In the articles referred to as summarizing piroplasmatic diseases no mention seems to be made of exactly similar regular conditions in cattle, sheep, and dogs. Starcoviç, however, refers to a "jelly-like, hemorrhagic, subcutaneous edema" in hemoglobinuria of cattle and "a yellow jelly-like edema, here and there under the skin" in carceag of sheep. Smith reports, for Texas fever, that "the skin presents nothing abnormal to the unaided eye. \* \* \* In one case the hair on the abdomen and the inner aspect of the thighs was matted into little tufts by dried blood; the skin showed at such places a bluish elevated spot, and when incised a little blood was found in the subcutis; this may be what has been called blood sweating."

If "spotted fever" is a piroplasmosis, we would therefore seem to have in man a skin lesion which marks this disease as quite different, clinically, from similar diseases in other animals.

#### DESQUAMATION.

*Idaho.*—A brownish desquamation is usual about the third week; subjects that die at this stage present a resemblance to smallpox, due to the loss of epidermis from the apices of the papules (Bowers, 1896, p. 63). Figgins (1896) gives the third or

fourth week as the time of desquamation. According to Maxey (1899, p. 436) the desquamation during convalescence is somewhat peculiar, and can best be studied on the feet; the spots seem to cause a circumscribed death of the skin. A short time ago he examined Mr. D., one of his spotted-fever cases, who was taken sick 2 months previously; patient was sick 18 or 20 days, and made a rapid and perfect recovery. It was a warm day; he had taken a brisk walk just before coming to the office, and when stripped for examination spots could be dimly seen in the skin on the hands and feet, but none on the body. On the soles of the feet were many round, white areas of dead epidermis, corresponding to the former location of the spots, and when this dead epidermis was removed it gave to the thick skin of the sole a punched-out appearance. Over the body desquamation is hardly noticeable, but it does occur.

*Montana*.—McCullough (1902, p. 227) reports a peeling of the eruptive spots upon patients who recover. According to Wilson and Chowning (1902a, p. 132; 1903a, p. 63; 1904a, p. 38), desquamation begins about the third week and extends over the whole body, but is slight except over the most affected areas. Anderson (1903c, p. 23) agrees that when convalescence is well advanced desquamation begins and extends over the entire body.

#### JAUNDICE.

In addition to the eruption the skin takes on a congested, jaundiced appearance, well marked in the conjunctivæ (Gwinn, 1902). According to McCullough (1902, p. 226) jaundice accompanies the majority of cases, depicted over the entire body, and well marked upon the conjunctivæ. According to Wilson and Chowning (1902a, p. 132; 1903a, p. 63; 1904a, p. 38) the skin ordinarily shows some jaundice. Anderson (1903a, p. 507; 1903c, p. 23) states that the skin is always jaundiced to a greater or less degree, first noticed in the conjunctivæ. He reports (p. 32) the skin of case 120 as distinctly yellow; on post-mortem (p. 33) deeply jaundiced.

In 1904 jaundice was noticed to a greater or less extent in practically all the Bitter Root Valley cases. It was reported especially in case 9 for skin and conjunctivæ.

COMPARISON.—Jaundice of the skin is reported for Texas fever as "of rare occurrence;" in dogs the skin becomes "icteric, may become chrome yellow in color;" icterus was "very slight or not evident" in dogs which Nuttall studied; icterus was noticed "in the mucous membranes of the eye, mouth, and skin in 30 out of 63 cases observed" in France. Icterus is not reported by Starovici for hemoglobinuria in cattle.

#### CYANOSIS.

The congested and cyanotic condition of the skin causes a bloated, stupid expression of the face in most cases, which is a very diagnostic symptom (Gwinn, 1902).

Case 11 (1904) showed cyanosis June 25-26 (seventh and eighth days).

#### GANGRENE.

*Idaho*.—Sloughing of the scrotum occurred in one case (Bowers, 1896, p. 63). Fairchild (1896) also reports occasional sloughing of limited areas, such as of the scrotum, etc.

*Montana*.—Gangrene is not an infrequent complication and may affect the fingers, toes, the region about the lobe of the ear, or in fact almost any part of the body; in one case the odor of the exhalations and sputum gave strong evidence of gangrene of the lungs (Gwinn, 1902). According to McCullough (1902, p. 226) gangrene frequently affects the toes, fingers, and dependent portions of the body. Wilson and

Chowning (1902a, p. 132; 1903a, p. 63; 1904a, p. 38) report that in some cases the skin becomes gangrenous over considerable areas, as on the elbows, fingers, toes, lobes of the ears, scrotum, etc. Anderson (1903a, p. 507; 1903c, p. 23) states that in very severe cases there may be gangrene of the fingers and toes, and still more frequently of the skin of the scrotum and penis; in case 120 the epidermis over scrotum sloughed off from an area about 2 to 5 centimeters in diameter (Anderson, 1903c, p. 33).

Gates (1905, p. 115) reports that in his case 6 (1900) the skin of the scrotum and legs became gangrenous before death, and Buckley noticed gangrene in case 1 (1904).

#### HYPERESTHESIA.

*Idaho*.—Bowers (1896, p. 64) reports hyperesthesia on the surface of the body.

*Montana*.—McCullough (1902, p. 227) says there is an exaggerated superficial hyperesthesia of the skin, as well as deep soreness, the patient fearing to be moved or touched.

In the cases observed in 1904, hyperesthesia was especially marked in Minshall's case (No. 8), and in Buckley's case (No. 2).

#### FAT.

See also Emaciation, page 74.

The panniculus adiposus was about normal in case 120 (Anderson, 1903c, p. 32).

In 1904, case 11, upon autopsy, showed a good amount of subcutaneous fat when incision was made from manubrium to pubis.

#### HEAD.

##### FACE.

*Idaho*.—Early in the disease the face acquires a dusky flush, and is slightly swollen; the expression becomes listless, dull, and heavy (Bowers, 1896, p. 63). Zipf (1896, p. 65) reports flushed face.

*Montana*.—The congested and cyanotic condition of the skin causes a bloated, stupid expression of the face in most cases, and this is a very diagnostic symptom (Gwinn, 1902). There is a glazed appearance of the face, bordering upon being copper colored, and taking a bluish or dusky hue as the disease advances.

In all severe cases more or less edema of the face and extremities is present. This may be marked, and may appear as early as the third day of the disease (Wilson and Chowning, 1902a, p. 133; 1903a, p. 64; 1904a, p. 40). There was considerable swelling of the legs and face the last day or two in cases 24 and 72 (Wilson and Chowning, 1903a, pp. 32, 37; Anderson, 1903c, pp. 13, 15); in cases 117 and 120 there was also more or less swelling of the face and limbs (Anderson, 1903c, pp. 27, 32).

Gates (1905, p. 111) reports the face of his case 14 as slightly flushed.

In 1904 the face of case 1 was reported as congested; of cases 8 and 10, flushed; of case 5, slightly flushed; of case 3, as placid, blotched with eruption, and then darkly flushed (May 13); of case 6, as florid; case 11, as dusky.

##### EARS.

Wilson and Chowning (1903a, p. 44) report ringing in the ears for case No. 109; the patient had been partially deaf for 2 or 3 days at the beginning of the sickness; case 89 (p. 49) experienced deafness (but had had quinine); deafness is also recorded for case 107. Anderson (1903c, p. 36) reports ringing in the ears in case 121.

## EYES.

See also Jaundice, page 50.

*Idaho*.—The conjunctivæ are more or less injected (Bowers, 1896, p. 63). The eruption in many cases, invades the eyes causing severe pain, and making them very sensitive to light.

*Montana*.—Jaundice is well marked upon the conjunctivæ (McCullough, 1902, p. 226; Gwinn, 1902). According to Wilson and Chowning (1902a, p. 132; 1903a, p. 63; 1904a, p. 38) jaundice may be quite marked in the conjunctivæ, the vessels of which are injected from the outset. Anderson (1903a, p. 507; 1903c, p. 21) says that jaundice is first noticed in the conjunctivæ, the vessels of which are congested from the outset.

The pupils react normally to light and accommodation (Wilson and Chowning, 1902a, p. 133; 1904a, p. 38; Anderson, 1903c, p. 23). Gates (1905, p. 111) reports the conjunctivæ of case 11 congested; eyes of his case 14 as dull, conjunctivæ slightly congested; case 15, conjunctivæ congested; case 16, eyes much congested.

In 1904, the conjunctivæ were reported as injected in case 8, but as not injected in case 13; the eyes were reported as injected in cases 2 and 10; in case 2 they were quite bloodshot on May 8; they were normal in case 3 on May 10; in case 1 the sclerotics were much injected.

Case 2 complained of sore eyes early in the attack; there was no tenderness of the eyeballs in case 11, but some hours before death the pupils were widely dilated, despite the fact that the patient was receiving large doses of morphine.

An examination of the eyes of case 9 by Gwinn showed the media a little blurred, so that the granular appearance of the retina could not be seen; the larger retinal blood vessels were quite plain, however; there was no swelling or blurring of the disk; no hemorrhagic petechiæ in the retina.

In case 10 there was a slight convergent strabismus; on June 10, the mother states that last night patient cried out that his eyes were turning out; she examined, and saw that a divergent squint (outward rotation) of the left eye was present; this later disappeared; the eyes were suffused. The pupils in case 13 were reported as dilated and irresponsive to light. In case 8 the eyes reacted to light up to May 28.

## PHOTOPHOBIA.

*Idaho*.—In many cases the patient is very sensitive to light (Fairchild, 1896). Dubois, (1896, p. 64) also reports photophobia. In one case two years elapsed before sunlight was borne without intense cephalalgia (Bowers, 1896, p. 63).

*Montana*.—Wilson and Chowning (1903a, p. 46) report photophobia for case 107. Gates (1905, p. 113) reports photophobia for his case 16 (1904).

In 1904 photophobia was more or less present in cases 2 to 11, except possibly case 8. It was especially marked in cases 2 and 10.

## NOSE.

## EPISTAXIS.

See also Hemorrhage, page 63.

*Idaho*.—Epistaxis occurs in some cases (Figgins, 1896, p. 64).

*Montana*.—Epistaxis is present (McCullough, 1902, p. 227) and not uncommon



(Gwinn, 1902). Two physicians have noted epistaxis; it was not observed in 1902, but was seen in 3 cases in 1903 (Wilson and Chowning, 1903a, p. 65; 1904a, p. 40). According to Anderson (1903c, pp. 21, 23, 32, 36-37), however, nosebleed is always present, usually from the end of the first week, and is sometimes quite severe; he reports it for cases Nos. 120 and 121.

In 1904, nosebleed was reported as not present in case 9; slight in case 6; frequent, but not excessive, during last five days in case 7.

#### MOUTH AND THROAT.

See also Cough, page 71.

*Idaho*.—Sore mouth and congested fauces are met with (Bowers, 1896, p. 64). Many cases suffer from congestion of the throat, which is very sensitive and painful and interferes with swallowing (Fairchild, 1896).

*Montana*.—The mouth is parched and dry (McCullough, 1902, p. 227); there was a bad taste in the mouth in case 89 (Wilson and Chowning, 1903a, p. 49); also in case 120 (Anderson, 1903c, p. 30). Gates (1903, p. 48) reports sore throat in one case. Wilson and Chowning (1903a, p. 49) report intense thirst in case 89.

In 1904, the lips were dry, blood stained, and crusted in cases 2 and 7; sordes were present on lips and tongue in case 11.

There was no eruption in the mouth or throat in cases 3, 9, and 10.

In case 3 the fauces and pharynx were much injected and showed adherent mucus-pus.

Sore throat was not noticed in cases 7 and 10; in case 2 there was marked irritation in the throat, and it was very sore to the touch; in case 3 the throat was at one time very sore, but it improved later; in case 5 the throat was slightly sore, but showed no marked injection; in case 5 sore throat was an early symptom; in case 8 the throat was slightly sore.

In case 2 there was marked huskiness of voice.

In cases 2 and 8 there was intense thirst.

*Comparisons*.—The pharynx and larynx are hyperemic in hemoglobinuria, and the mucosa is swollen in carceag.

#### BREATH.

Gwinn (1902) states that in one case the odor of the breath gave evidence of gangrene of the lungs. Anderson (1903c, p. 29) reports a peculiar sweetish odor to the breath in case 120.

In 1904, case 3 presented an unusually offensive breath, which during the last stages became absolutely nauseating; the breath of this patient during health was said to be very offensive. Cases 9 and 11 presented a more or less urinous odor to the breath.

#### TONGUE.

*Idaho*.—Bowers (1896, p. 64) reports the tongue as thick and furred. Collister (1896, p. 63) says that it is usually covered with a whitish or yellowish fur, but in severe typhoidal cases is dry, red, and glazed. Fairchild (1896) describes it as coated by a whitish fur with red edges early in the disease; later, the whitish coat usually disappears and the tongue becomes red and frequently dry and brown or black. Springer (1896, p. 62) says that the tongue has a yellowish-white coat with

red edges; in the later stages it becomes red, or dry and brown. According to Springer (1896) the tongue is always coated, a thin, white fur persisting for a long time. Zipf (1896, p. 65) also reports coated tongue. Maxey (1899, p. 435) reports the tongue as at first covered with a whitish coating, but about the time the fever reaches its maximum the tongue changes to a dry, brownish condition, which continues until the general symptoms begin to ameliorate, when the tongue clears in an irregular manner, beginning at the base.

*Montana.*—According to Gwinn (1902) the tongue at first has a white coat, but it soon becomes brown and is accompanied by sordes. Wilson and Chowning (1903a, pp. 44, 46, 62; 1904a, p. 37) describe the tongue as dry with heavy white or yellowish coat in the middle, but red at the tip and along the edges; it may be thickly coated even at the onset (1902a, p. 132); while the coat is whitish at first, it becomes brownish as the fever progresses, and the tongue may become dry and cracked (1902a, p. 132). Anderson (1903a, p. 21, 23, 29, 31) agrees that at first the tongue has a heavy, whitish coat with red edge and tip; later it becomes dark brown; in case 117 it was coated throughout the disease; in case 120 it was furred on April 29, and on May 6 it showed a heavy white coat with red tip and margins; in case 121 it had a heavy white coat in the center with red tip and edges. Gates (1903, p. 49) says in regard to one case when first seen that the tongue was coated white on the sides and was rather dry.

In 1904 the tongue was moist in case 1; tremulous and with a heavy white moist coat in case 3; it had a heavy white moist coat in cases 5 and 10; in case 8 there was a heavy white coat, which became dry and brown; in case 7 there was a heavy moist coat which became dry, brown, and somewhat glazed; in case 9 the tongue was heavily coated; in case 11 it was red and moist, with white streaks; in case 13 the tongue was furred.

Gates (1905, p. 111) reports that in his case (11) the tongue quivered very much when extruded, and it was loaded with a heavy dirty-brown coat, the sides of the tongue were so livid as to be almost blue; his case (14) showed a grayish coat on the tongue; in his case (16) the tongue became very dry early in the disease.

#### TEETH.

Gwinn (1902) and McCullough (1902, p. 227) say that sordes are present. Wilson and Chowning (1902a, p. 132; 1903a, p. 62; 1904a, p. 37) state that sordes appear early and may be quite pronounced. Anderson (1903c, p. 23) also agrees that the teeth may be covered with sordes.

#### NECK.

In case 109 there was no stiffness of the muscles of the neck and back, though some pain was present on pressure over the spinal process of the vertebrae, especially in the dorsal lumbar region. (Wilson and Chowning, 1903a, p. 45.)

In case 115 the postcervical glands were enlarged, particularly on the right side; in case 116 the axillary glands were swollen and sore the day after the tick bite; in case 120 the mesenteric and retroperitoneal glands were pale, but not enlarged (autopsy).—Anderson, 1903c, pp. 24, 25, 33.

In 1904, case 9 showed no stiffness of the neck, and the head could be readily bent forward; in case 6 there was general rigidity of the

body on May 20; in case 7 there was cervical tenderness on first day of illness; case 11 had cervical tenderness for several days.

In cases 3 and 10 the cervical glands were somewhat enlarged.

#### ABDOMEN.

There was considerable gurgling and tenderness in the right iliac fossa in case 120 (Anderson, 1903c, p. 31); tympanites is never excessive (1903c, p. 23). Anderson (1903c, p. 120) reports the mesenteric and retroperitoneal glands as pale and not enlarged. Abdominal tympanites usually appears 1 or 2 hours before death. (Wilson and Chowning, 1904a, p. 40.) Gates (1905, p. 111) reports tympanites as moderate in his nonfatal case 11 on the 10th day.

In 1904, the abdomen was not distended or painful in case 3 (May 10, 1904); it was generally tender, especially on right side in case 8 (May 26, 1904), and was painful and tender in case 10.

Autopsy of case 11 (1904) showed the abdominal organs in normal relation and position.

#### PERITONEUM.

In case 11 (1904), the peritoneum was normal; there was a considerable amount of straw-colored material present in peritoneal cavity.

COMPARISONS.—In hemoglobinuria the peritoneum near the duodenum is always yellowish and jelly-like, swollen and ecchymotic.

#### OMENTUM.

In case 97 the omentum was somewhat discolored, showing postmortem degeneration; in case 94 it was slightly hemorrhagic. (Wilson and Chowning, 1903a, pp. 56-58.)

See also page 68.

#### EXTREMITIES.

*Idaho*.—Bowers (1896, p. 63) speaks of swollen joints, the joint lesions developing with the spots; the swelling disappears during the period of absorption and convalescence.

In 1904 the knee jerks were normal in case 10; patellar reflex was exaggerated and ankle clonus pronounced in case 13.

In case 2 the finger nails turned purple about half an hour before death.

#### GENTILIA.

See also page 50.

Bowers (1896, p. 63), reports that the scrotum and testicles are swollen in severe cases. Fairchild (1896) and others say that sloughing occasionally takes place over limited areas, such as of scrotum, etc.

#### DIGESTIVE SYSTEM.

##### MOUTH, TONGUE, TEETH.

See pages 53-54.

##### APPETITE.

*Idaho*.—The loss of appetite is early and the relish for food is not regained until the patient is quite convalescent (Bowers, 1896, p. 63). Dubois (1896, p. 64) reports persistent anorexia. In many cases the appetite is lost (Fairchild, 1896). There is

first a loss of appetite, but after the first 5 or 6 days in many cases it returns and remains good throughout the attack (Maxey, 1899, p. 435).

*Montana*.—McCullough (1902, p. 227) reports an apathy for food and nourishment. Wilson and Chowning (1902a, p. 133; 1903a, p. 64; 1904a, p. 40) state that at the onset of the disease the appetite is usually good and food is well retained and assimilated. Anderson (1903c, p. 23) gives the appetite as often good throughout the first week. Gates (1903, p. 48) reports it as completely absent in one case when first seen; in another case food and medicine were taken well until the last 36 hours. He (1905, pp. 111-116) reports loss of appetite for cases 11, 14 (complete), and 15.

In 1904, appetite was fairly good in case 8 on May 22; in case 4 there was complete loss of appetite on May 13; appetite was absent in cases 5 and 7, in the latter case throughout the attack; case 6 had difficulty in swallowing (May 20).

COMPARISON.—For Texas fever, Smith and Kilborne (1893, p. 20) report that loss of appetite always, and cessation of rumination usually, accompany the high fever after the third or fourth day. Loss of appetite is also reported for hemoglobinuria in cattle. Nuttall (1904, pp. 232-233) records for canine piroplasmiasis that loss of appetite is a constant and early symptom, observed in all cases upon which he has experimented. The dogs refuse all food in later stages; they may drink much water but refuse milk (Hutcheon, 1899). This symptom is also noted by Lounsbury and Robertson. In France loss of appetite is noted at onset in acute cases, and the appetite is not regained; anorexia is also observed in chronic cases.

#### STOMACH.

*Idaho*.—Springer (1896, p. 62) reports irritability and severe pains in the stomach. In some cases (Fairchild, 1896) it shows marked irritability.

*Montana*.—Anderson (1903c, p. 38), in his summary of lesions, reports the stomach as normal, but he says (p. 33) that in case 120 it was apparently normal, except hypostatic congestion over dorsal surface of fundus. Wilson and Chowning (1904a, p. 41) say that in some cases the dependent portions of the stomach were hyperemic.

In 1904 "stomach ache" was reported as absent in case 5 but present in case 7. "Cramps in stomach" were reported for case 2.

Upon autopsy, case 11 (1904) showed injection about cardiac end, otherwise it appeared normal.

See also page 57.

#### NAUSEA AND VOMITING.

*Idaho*.—Nausea is common, and vomiting an occasional symptom (Bowers, 1896, pp. 63-64). Collister (1896, p. 63) says that nausea and vomiting are present until the fourth or fifth day of the fever. Dubois (1896, p. 64) reports nausea as an early symptom.

*Montana*.—Vomiting may be present to a greater or less degree (McCullough, 1902, p. 227). About the beginning of the second week nausea and vomiting develop and continue in fatal cases to the end; in some cases nausea is present from the onset (Wilson and Chowning, 1903a, p. 64; 1904a, p. 40). According to Anderson (1903c, p. 23) there may be at first a little nausea, but the appetite is often good throughout the first week; in fatal cases nausea becomes more persistent during the second week and lasts until the end; he reports (1903c, pp. 16, 34) vomiting as an initial symptom in case 97, and nausea present in case 121. Gates (1903, p. 49) reports vomiting once in one case; he (1905, pp. 111) reports vomiting for his case 11, but there was no vomiting in his case 16, who took food well at all times.



In 1904, nausea was reported as present in case 7, absent in cases 5 and 8. Vomiting was noticed twice (May 5) in case 2; case 5 vomited practically everything taken; case 7 vomited throughout the attack, the vomit being greenish-yellow and containing blood (May 20), thought to be from nose; cases 10 and 11 vomited early in the attack.

#### INTESTINES.

Wilson and Chowning (1904a, p. 42) report the intestines as normal upon post-mortem, except slight hypostatic congestion in two cases, throughout their entire extent.

The stomach and intestine were normal in case 91. In case 93 the stomach was congested (hypostatic?) over dorsal portion; intestine normal. In case 97 intestine was slightly discolored and distended by gas. In case 107 there was nothing abnormal except that the colon was distended by gas. In case 89 there was nothing abnormal except a slight congestion (probably hypostatic) in upper portion of the jejunum. In case 94 nothing abnormal except intestine distended with gas (Wilson and Chowning, 1903a, pp. 48, 51, 54, 56, 58). In case 120 the small intestine was empty and showed no inflammation or congestion except hypostatic (Anderson, 1903c, p. 33).

None of the glands were enlarged in cases 89, 91, 93, 107; Peyer's patches pale and not congested in case 120.

The mesenteric vessels were congested in case 93.

In case 11 (1904) the upper portion of the intestine appeared normal; solitary glands and Peyer's patches appeared somewhat swollen; cecum showed considerable injection, which continued more or less throughout the colon.

COMPARISONS.—Smith and Kilborne (1893, p. 34) state regarding Texas fever that "The lesions of the intestines are limited to hyperemia and pigmentation. Beginning with the duodenum, there is found generally an abundance of bile and more or less injection and pigmentation of the villi appearing in the form of closely set points and fine lines. The remainder of the small intestine may show with the stomach more or less marked congestion, or there may be patches marked by the injection of minute vessels. In many of the cases examined the mucosa was pale and concealed by a thin layer of a grayish pasty consistency made up largely of desquamated epithelium. \* \* \* In the large intestine we find more or less hyperemia and pigmentation in longitudinal lines corresponding to the summits of the folds of the mucous membrane. This condition is more marked in the cæcum and rectum than in the colon and seems to be associated with the constipated condition. Thus the cæcum is in some cases distended with very hard, dry, fecal balls and some may be found in the rectum. In some cases no abnormal condition of the large bowel is discoverable."

For hemoglobinuria of cattle Starcovič says that in the duodenum ecchymoses or small ulcers are constant; the mucosa of the small intestine is always much swollen and covered with a thick, yellowish jelly-like mass; the mucosa of the large intestine constantly shows ecchymoses and swelling. In carceag the rectum contains hard or soft slimy masses of manure mixed with blood; the mucosa regularly has extensive hemorrhages along the folds, and the bases of the folds are covered with a crumbling or pulpy, dirty brown scab.

In canine piroplasmiasis there is a catarrhal inflammation of the small intestine, more intense about the duodenum; the lumen contains a viscid mucus often mixed with blood; the large intestines are slightly but not uniformly inflamed, and contain much viscid mucus (Hutcheon). Mucosa is infiltrated and congested on a level with the duodenum in a few cases.

*Idaho.*—The bowels, as a rule, are constipated and the abdomen retracted, but occasionally marked diarrhoea occurs; there is no tympanites or tenderness of the abdomen (Fairchild, 1896). Bowers (1896, p. 64) reports constipation as usual during the entire illness. According to Figgins (1896, p. 64) the bowels are either constipated or quite loose; in some cases typhoid symptoms in malignant form are noticed. Springer (1896, p. 62) says that the bowels, as a rule, are constipated, and Sweet (1896, p. 61) agrees that constipation is usual, although diarrhoea sometimes occurs. Maxey (1899, p. 435) states that the bowels remain constipated throughout the entire course of the disease.

*Montana.*—Most of Gwinn's cases (1896) were suffering more or less from indigestion and constipation at the time of the attack. According to Wilson and Chowning (1903a, p. 64; 1904a, p. 40) constipation is usually present from the beginning. According to Anderson (1903c, pp. 23, 29) constipation is present throughout the course of the attack: tympanites is never excessive; there is occasionally gurgling in the right iliac fossa. In case 119 improvement was interrupted by attack of acute indigestion. Constipation is reported for cases 118 (p. 27) and 121 (p. 36). Bowels were loose from the onset in case 97 (p. 16), and they were regular after initial constipation in case 117 (p. 27).

In one case (Gates, 1903, p. 49) a number of watery evacuations were produced by the action of elaterium. Gates (1905, pp. 111-112) reports constipation present in his cases 14 and 15; in case 14 the bowels became loose later.

In 1904 the bowels were at first normal in case 3, but after use of salt enemata they became loose (May 10); case 5 was at first slightly constipated, but the bowels afterwards became normal (May 18); in case 6 nothing abnormal was noticed; in case 7 they acted regularly and without assistance, there was no diarrhoea; in case 10 they were loose; case 13 was constipated.

In two cases I examined microscopically for intestinal parasites, with negative results.

*COMPARISONS.*—In Texas fever the bowels are as a rule constipated during the high fever, and on post-mortem examination the large bowels (cecum and colon) are found in some cases compactly filled with small, very firm, hard balls of dung. As the fever subsides the feces again become softer and are then found more or less deeply tinged with bile. In hemoglobinuria of cattle there is colic, constipation, with hard feces surrounded by bloody mucus. In carceag there is colic, and hard, bloody stools.

#### LIVER.

*Size.*—Gwinn (1902) reports slight enlargement of the liver in one autopsy.

The liver is somewhat, though not markedly, enlarged (Wilson and Chowning, 1902a, p. 133); pain on pressure is absent (1904a, p. 40); pale in color and of normal consistency (1904a, p. 42); the capillaries are distended with blood containing an excess of leukocytes; many red cells contain parasites; the infected cells are frequently contained within phagocytes; there is acute parenchymatous hepatitis, with very marked fatty degeneration; some of the cases show considerable blood pigment.

Anderson (1903c, pp. 23, 31, 33, 36, 38) reports the liver as normal or usually slightly enlarged; pale, fatty in appearance; in parts areas are outlined by bile pigment; in some areas outlined by enlarged bile ducts; sections usually show fatty infiltration, bile capillaries full.

Wilson and Chowning (1903a, pp. 48, 51, 53, 54, 56, 58) report the liver as normal in size for case 94, rather swollen for case 97, appreciably enlarged for case 91, some-

what enlarged for 89, enlarged though not markedly so for case 93, noticeably enlarged for case 107. Anderson (1903c, p. 33) reports the liver as enlarged (weight 92.5 ounces) for case 120.

In 1904 the liver was not enlarged (on May 10) in case 3; in case 11, on post-mortem, it was apparently somewhat enlarged.

COMPARISON.—In Texas fever and hemoglobinuria the liver is reported as enlarged. In canine piroplasmiasis the liver may be normal in size in acute cases or in some cases it may be enormously enlarged.

*Color.*—The liver was apparently normal in color in cases 94, 97; it was paler than normal in cases 89, 91, 107, and quite pale in case 93 (Wilson and Chowning, 1903a, pp. 48, 51, 53, 54, 56, 58); it was pale also in case 120 (Anderson, 1903c, p. 33).

In 1904, the liver was paler than normal in case 11, with yellowish tinge, apparently due to fat.

COMPARISONS.—In Texas fever the color of the surface is usually paler than in normal livers, and in most cases of a peculiar mottled appearance. The mottling is due to minute irregular grayish-yellow patches, usually 1 mm. or less in diameter. Starcovici reports the liver as pale and marbled in hemoglobinuria and pale in carceag. Nuttall reports, in reference to canine piroplasmiasis, that the liver in an acute case was yellowish; it is usually congested, at times inflamed, and of mahogany or saffron color.

*Section.*—In case 97 the liver cut easily and was quite light in color on section; in case 107 it was of normal consistency and showed no congestion; in case 89 it showed no adhesions, and in cases 89, 91 it was of normal consistency and was not congested; it was normal in consistency in case 93 (Wilson and Chowning, 1903a, pp. 48, 51, 53, 54, 56, 58). In case 120 it was fatty in appearance, and in some areas outlined by engorged bile ducts (Anderson, 1903c, p. 33).

In 1904, section of the liver of case 11 was decidedly pale. What little blood flowed was also very pale; tissue was firm but apparently not fibroid.

COMPARISON.—In Texas fever, when incised, the parenchyma of the liver was remarkably bloodless in most cases, and a lac-colored thick blood poured from the cut ends of the larger hepatic veins; the color of the cut surface was either a uniformly brownish-yellow or else mottled as on the surface; the mottling, on closer scrutiny with the naked eye or hand lens, was found to be due to a paler yellowish discoloration of the zone bordering the intralobular veins; this zone of discoloration was the wider the more prolonged the disease, and in a few cases involved the entire lobule; parallel to this degenerative process the consistency of the organ became less resistant, more doughy, and brittle. In thin razor sections of fresh tissue the most striking phenomenon was the filling up of the ultimate bile canaliculi so that the hepatic cells were inclosed in polygons of yellow lines forming a beautiful network; when the liver is teased and crushed, the contents of these bile canaliculi may be found floating free in the form of rods, sometimes with Y-shaped ends; this stasis or filling up of the ultimate bile capillaries was present in nearly all animals examined; it was most pronounced in those whose death followed quickly after a high fever; in one case killed in the early days of the fever the liver was the seat of marked congestion, the bile stasis not having taken place yet. The extent of this stasis varies considerably. It may be seen in small isolated areas or else it may involve a large continuous territory. Owing to absence of connective tissue between the lobules it is quite impossible in fresh sections to make out accurately its distribution. It seems to be most frequently met with in the innermost or hepatic zone of the lobule, but it may also be found involving the entire lobule.



Small bile ducts between the lobules are often found injected, and rarely lines of yellow injection may be visible to the unaided eye.

“Associated with the occlusion of the biliary canaliculi and ducts is a more or less extensive fatty degeneration of the hepatic cells. This is most advanced in prolonged cases of disease. In several which came under our observation the fatty changes were so extensive that cells free from large quantities of fat could not be seen. Among other abnormal appearances may be mentioned the presence of irregular yellow clumps of pigment in the hepatic cells and of stellate masses or blood-red needle-like crystals of very minute size. In one case large branched thrombi were found in some of the hepatic veins. \* \* \* The injection of the bile canaliculi is seen only in Müller’s fluid preparations or in alcoholic material cut directly without imbedding. The extent and location of the injection are variable. It may appear over an entire lobule or only a small portion of it. The fatty degeneration so regularly seen in fresh material shows itself in sections of hardened material in a peculiar vacuolated appearance of the cell protoplasm, the fat having been dissolved out. The vacuolation may be more pronounced near the center of the lobule, where the individual vacuoles may be as large as red corpuscles. Of these there may be several in a single cell, very little of the protoplasm remaining. The cell protoplasm of the peripheral zone of the lobule is uniformly vacuolated, the vacuoles being very small.

“Another change that is of considerable importance in estimating the pathological effect of the disease is a tendency toward necrosis of the inner zone of the lobule. This process, which shows itself to the naked eye as a faint paler mottling of the liver tissue limited to the inner zone of the acini, seems to begin around the central vein and extend toward the periphery. It is characterized by a degeneration and loss of the nuclei of the parenchyma cells.” Smith and Kilborne, 1893, pp. 28-30.

Starocvici reports for hemoglobinuria that the center of the lobule is necrotic with gall stasis. In carceag the liver is friable; the finer changes of the liver consist in a collection of leukocytes, and the larger vessels show here and there gall stasis, and there is parenchymatic degeneration and fatty degeneration of liver cells, especially in the center of the lobes.

Nuttall reports for canine piroplasmiasis that his cases showed but slight gross changes.

#### GALL BLADDER.

In case 107 the gall bladder and its contents appeared normal; in case 93 it was distended with fluid bile; in case 94 it contained 1.5 ounces of fluid of a dark yellow color, and the gall ducts were patulous (Wilson and Chowning, 1903a, pp. 48, 54, 58).

In case 11 (1904) the gall bladder was distended with fluid bile, the ducts were patulous; there were no gallstones.

COMPARISON.—In Texas fever the bile is found in the gall bladder in considerable quantity (one-half pint to a quart) after death. As might be anticipated from the description of the changes in the liver, this fluid is greatly altered. The usual limp greenish fluid is replaced by an almost semisolid mass. As it flows from the incised bladder it has been aptly compared to chewed grass. The presence of mucus makes it cohesive enough to be drawn out into long flat bands as it flows. When it is allowed to stand quietly in a cylindrical vessel a layer of flakes settles down, which occupies not infrequently one-half of the entire column. The supernatant fluid is much darker than normal bile. The suspended matter appears to be made up chiefly of small yellowish flocculi or flakes. A deep-yellow tinge is imparted to all vessels and to the hands coming in contact with it. When examined under the microscope the suspended particles are resolved into amorphous yellowish masses mingled with bright golden points barely visible at 500 diameters. The common bile duct has



always been found pervious, and in many cases an abundance of bile is found in the small intestine (Smith and Kilborne, 1893, p. 31).

For bovine hemoglobinuria, Starcovici states that there is thick, dark bile in the gall bladder.

In canine piroplasmosis the bile is usually thick, sirupy, grumous or dark green, and distends the gall bladder.

Thus, if "spotted fever" is a piroplasmosis, the disease differs in its effects upon the gall of man from the effects shown in bovine and canine piroplasmosis.

#### PANCREAS.

Anderson (1902, pp. 33, 38) states that the pancreas is about twice its normal weight; in case 120 it was normal in appearance, except enlargement (5 ounces).

In case 11 (1904) the pancreas was apparently normal.

#### CIRCULATORY SYSTEM.

##### HEART.

Upon autopsy, the epicardium usually contained a few petechial hemorrhages near the base of the left ventricle; pericardium was normal; the myocardium was softened; the right ventricle was filled with dark fluid blood, the left was almost empty or contained only a small clot; the capillaries of the heart are distended; there is not much extravasation of red cells, but considerable round-cell infiltration; all the cases show considerable parenchymatous degeneration; those cases in which round-cell infiltration is marked also show swelling of the muscle-fiber nuclei with fragmentation (Wilson and Chowning, 1904a, pp. 41, 42).

*Pericardium.*—The pericardium was normal in cases 107, 89, 91, 93, 97, and 94 (Wilson and Chowning, 1903a, pp. 48, 51, 52, 54, 56, 58); also in case 120 (Anderson, 1903c, p. 33).

The pericardial cavity contained an excess of fluid in cases 107 and 91 (Wilson and Chowning, 1903a, pp. 48, 51); fluid was not increased in cases 93 and 97 (1903a, pp. 53, 56), and about 2 ounces of fluid was present in case 120 (Anderson, 1903c, p. 33).

In case 11 (1904) there was an apparent excess of clear, straw-colored fluid.

*Epicardium* contained no hemorrhagic areas in case 107; in case 93 it showed on ventral surface of left ventricle several small hemorrhagic areas (Wilson and Chowning, 1903a, pp. 48, 54).

There were no ecchymotic areas over the surface of the heart in case 89; in cases 97 and 94 there were hemorrhagic areas over both ventricles; in case 91 there was one small ecchymotic spot in the right ventricle (Wilson and Chowning, 1903a, pp. 51, 53, 56, 58). In case 120, there were a few small hemorrhages over the left ventricle near the interventricular groove under the pericardium; small chicken-fat clots were found in the auricles (Anderson, 1903c, p. 33).

The heart was normal in size in cases 107, 97, and 94 (Wilson and Chowning, 1903a, pp. 48, 56, 58); it was somewhat dilated in case 89 (1903a, p. 51).

In case 11 (1904) the heart was distended with blood; in general, it seemed normal.

The muscle was normal or perhaps a trifle softened in case 107, apparently somewhat softened in cases 91, 93, and soft in case 97 (Wilson and Chowning, 1903a, pp. 48, 53, 54); much softened and pale in case 89, soft in case 97 (1903a, pp. 51, 56). In case 120 the myocardium of the right heart was somewhat pale and flabby (Anderson, 1903a, p. 33).

In case 11 (1904) the muscle was well nourished.

The right side contained dark-red blood in case 107, dark fluid blood in case 89; blood in cases 91 and 93 apparently darker than normal (Wilson and Chowning, 1903a, pp. 48, 51, 53, 54). In case 120 the right heart was half filled with blood (Anderson, 1903a, p. 33).

In case 11 (1904) the right side contained small clots, white and red.

The left heart was contracted and empty in cases 107 and 89; it was empty in case 91; there was small clot in left heart of case 93 (Wilson and Chowning, 1903a, pp. 48, 51, 53, 54).

In case 11 (1904) the left ventricle was partially contracted and contained chicken-fat and red clots.

In case 97 the valves were normal (Wilson and Chowning, 1903a, p. 56).

In case 11 (1904) the valves of both sides were apparently normal.

The endocardium was normal in case 94 (Wilson and Chowning, 1903a, p. 58) and 120 (Anderson, 1903c, p. 33).

Gates (1905, pp. 111-113) reports that heart sounds were normal in case 14; the heart action was weak in case 16 from first day and became very weak and irregular, with low arterial pressure.

In 1904 the heart sounds were clear and normal in cases 3, 5, 7, and 11.

COMPARISON.—In Texas fever at autopsy the right ventricle is always distended with blood, fluid or clotted, according to the time elapsing between death and the examination. The left ventricle is usually firmly contracted and may contain a small quantity of fluid or clotted blood. The clots are quite firm and very rarely mixed with firmer, pale-yellowish clots. A very constant lesion is the extravasation of blood beneath the epicardium and endocardium. This is mainly restricted to the left ventricle, although petechiæ are not infrequently met with on the right ventricle. On the external surface of the heart the petechiæ are usually grouped along the interventricular groove and near the base, although cases occur in which the whole ventricular surface is sprinkled over with them. The inner surface of the left ventricle shows larger patches of extravasation, usually on or at the base of the papillary muscles. On the large vessels at the base of the heart within the pericardial sac there are frequently very delicate shreds of tissue or patches in a hyperæmic condition. The heart muscle, on closer inspection, is observed to have its minute vessels markedly injected, and in fresh sections the capillary network is found densely packed with red corpuscles. In cases which have succumbed after the subsidence of the fever the heart muscle is quite pale. Cloudy and fatty changes of the fibers are in some cases quite marked, in others absent or restricted to a small number of fibers (Smith and Kilborne, 1893, p. 26).

In carceag the pericardium and pleura usually show abundant ecchymoses.

In canine piroplasmosis the pericardium contains a variable amount of serous fluid; ecchymoses are around the heart, largely in left ventricle (Hutcheon); in France it is reported that the pericardium contains yellow or bloody fluid; not infrequently one observes numerous petechiæ about the apex or beneath the endocardium of the left heart; the heart may be pale (acute case).

#### AORTA.

In case 11 (1904) the arch of the aorta seemed unusually small.

## PULSE.

*Idaho*.—The pulse is more or less accelerated, often greatest at the beginning of convalescence; in the onset it is sluggish and lacks force; in fatal cases it is not usually greatly quickened; it may be slower than in health (Bowers, 1896, p. 63). Collister (1896, p. 63) says that it does not run very high, not often above 110 in adults. Fairchild (1896) reports it as usually slow and full, from 85 to 110. Springer (1896, p. 62) gives it as 100 to 130 in ordinary cases. Maxey (1899, p. 435) reports it from 80 to 120 per minute, at first full and bounding, later becoming soft, but not irregular.

*Montana*.—At first the pulse is full and strong, it gradually gains in rapidity and loses in strength and volume (Gwinn, 1902). According to McCullough (1902, p. 226) the pulse varies from 80 to 120 in typical cases, and lacks volume and regularity as the disease advances. Wilson and Chowning (1902a, p. 133; 1903a, p. 63; 1904a, p. 38) say that at the onset the pulse is usually full and strong, but gradually becomes more and more rapid while it loses in volume and strength, very much as in diphtheria; in fatal cases in adults it may reach 150 per minute some days before death; the rapidity of the pulse is sometimes out of all proportion to the temperature, as may be also the respiration.

Anderson (1903a, p. 507; 1903c, p. 22) reports that the pulse appears out of all proportion to the temperature, usually running from 110 to 140. A pulse of 120 is not unusual with a temperature of 102°; it is rather thready, though sometimes full and strong, occasionally dicrotic in the first week (1903c, p. 22). In case 120 (1903a, p. 29) the circulation was feeble on compressed areas and extremities.

Gates (1903c, pp. 48, 49) reports 186 as the highest pulse rate observed; one case at the end of the first week was almost pulseless; he reports (1905, p. 112) slow pulse and repeated chills as special features of his case 14.

COMPARISON.—In Texas fever the pulse and respiration rise with the fever. \* \* \* As the fever subsides and recovery begins the great weakness of the animal still keeps the pulse very high for a time, especially when the animal is moved about or excited in any way. The respirations, on the other hand, are apt to fall below the normal in this same period. When death approaches the heart beats increase in number as they grow feebler, and the respirations fall with the body temperature below the normal. (Smith and Kilborne, 1893, p. 18.)

In canine piroplasmiasis the pulse is weak and rapid; in acute cases it beats 120 to 160 a minute, is thready, and often intermittent.

## HEMORRHAGE.

See also Epistaxis, page 52.

There is a marked tendency to hemorrhage—nose, throat, lungs, and bowels, each have been known to be affected, and the blood loses power of coagulation. (McCullough, 1902, p. 226.)

## BLOOD.

Referring to their table, Wilson and Chowning (1904a, pp. 39, 40) conclude that the blood shows a marked reduction of red blood cells and hemoglobin, with a slight increase of leukocytes at times; the reduction of red cells is particularly marked just before death in fatal cases, and in recovering cases just before convalescence. Preparations taken from organs at autopsy, as well as those from the living patient, show a marked poikilocytosis and anemia. (Wilson and Chowning, 1903a, p. 67.)

None of the cases 1 to 11 (1904) were in a condition which would strike the observer as being anemic. A blood count might have shown some tendency to anemic condition, but from the general appearance of the patients such condition was not evident.



COMPARISONS.—In Texas fever, hemoglobinuria, carceag, and canine piroplasmosis, anemia is reported as present and in many cases as pronounced or intense. If "spotted fever" is a piroplasmosis, the action of the parasites in respect to anemia is far below the action of other members of the genus *Piroplasma*.

CONSISTENCY AND COLOR.

Gwinn (1902) took blood in five or six cases from the arm, and in all of them it was found to be dark and thick, with the power of coagulation partly or entirely lost; it regained a bright scarlet color upon being shaken up with the air. These facts, taken together with the frequent eruption, the frequent complication of gangrene, and the fact that the whole system seems to be affected, naturally would lead one to suspect the blood to be the part mostly affected. He also speaks of "the really thick unoxygenated blood."

Wilson and Chowning (1902a, p. 133; 1903a, p. 64; 1904a, p. 38) state that when removed for examination the blood appears somewhat darker than normal, as well as somewhat less fluid; on exposure to air the color brightens perceptibly.

In the Bitter Root Valley cases of 1904 the dark, thickened condition of the blood was a very prominent symptom. Not infrequently the blood was so thick and flowed so slowly as to be of some inconvenience in making blood smears. In case 3, I cut into a blood vessel within fifteen minutes after death, and the blood was so thick that I had to add salt solution in order to draw the blood into a syringe. In case 11, the blood was so thick about 12 hours before death that the operation of bleeding the patient was performed with difficulty.

COMPARISON.—For Texas fever, Smith and Kilborne (1893, p. 21) describe the blood as follows: "Another character of this disease, the most constant and valuable of all and of which the hæmoglobinuria or "red water" is but a part, is the thinness of the blood. \* \* \* Soon after the high temperature sets in the blood begins to grow thin, and after some days of fever it has become very pale and watery. \* \* \* The difference between the drop of rich red blood issuing from a slight cut of the skin in healthy cattle and the thin, pale drop oozing from such a cut in Texas fever is very marked. This difference is due to the loss of red corpuscles which give the blood its characteristic color. Associated with this there may be in some cases a marked bloodlessness of the skin in the later stages. A number of small incisions are often required to obtain a few drops of blood. In some cases, shortly before death, the blood slowly trickles from a slight incision for some time before it is checked by the natural process of coagulation.

"When freshly drawn blood is allowed to stand the serum forced out of the clot has in the acute stage a very dark-red color, indicating the presence of much coloring matter in solution. As regards the coagulability, which some observers have regarded as feeble, we have no facts pointing in one direction. In a few cases the coagulation appeared retarded; in others it appeared to be normal in rapidity and effectiveness. As will seen further on, the condition of the blood must vary considerably from time to time. At one time it may contain the débris of destroyed corpuscles equal in number to one-tenth, or even one-fifth, of all circulating in the body. That under such circumstances its coagulability may be affected is evident. Frequently, however, the blood comes under observation when the destruction of red corpuscles has ceased, and the products have either been excreted or metamorphosed. In this way conflicting observations may perhaps be harmonized. In general, we may say that the coagulability of the blood is not much altered."

Starcovici reports the blood in hemoglobinuria as pale and lac-colored.



Nuttall (1904, pp. 235, 236, 237) reports the blood in canine piroplasmosis as profoundly altered, pale and watery, and with coagulation retarded; the serum is tinged with hemoglobin.

The difference in the blood in "spotted fever" on the one hand, and in piroplasmatic diseases on the other hand, is thus seen to be quite marked. In a piroplasmosis we naturally expect to find marked changes in the blood; but from our present knowledge it would appear that in Texas fever, hemoglobinuria, and canine piroplasmosis these changes are in one direction (the blood becoming thin, watery, and pale), while in "spotted fever" they are in the opposite direction (the blood becoming thick, molasses like, and dark). If now "spotted fever" be a true piroplasmosis, it would seem that a genus (*Piroplasma*) of protozoa has very different effects upon the blood of man from those noticed in cattle and dogs.

Viewed from the consistency of the blood, the condition noted in "spotted fever" can not at present be said to support the theory that this disease is a true piroplasmosis.

#### RED CELL COUNT.

Wilson and Chowning (1902a, p. 133; 1903a, p. 64) appear to be the first to give the red cell count in this disease; they found it to be 4,100,000, 4,200,000, 4,300,000, 4,400,000, and 4,500,000, respectively, in 5 cases examined; they call attention to the fact that these counts were made in an altitude of about 3,500 feet, where the normal count is above rather than under 5,500,000; they give a table of counts (1904a, p. 39) for cases 89, 94, 107, 115-120, 122-124. Anderson gives blood counts for several cases and concludes (1903a, p. 507; 1903c, p. 22) that there is a progressive decrease in red cells, but as soon as the temperature becomes normal an increase begins.

COMPARISON.—In Texas fever there is a tremendous decrease in the red cell count. Thus, Smith and Kilborne (1903, pp. 38 to 41) report a decrease in acute cases from 6,290,000, July 31, to 2,025,000, August 28; 7,171,000, August 13, to 1,675,000, August 29; 5,000,000, August 13, to 2,645,000, August 25.

In the mild nonfatal type the decrease is slower.

For canine piroplasmosis Nuttall (1904, pp. 238-239) reports the following cases: Typical acute case, 5,240,000 first day to 2,200,000 late the fifth day; typical chronic case, 5,840,000 first day to 1,200,000 late the fifteenth day.

#### LEUKOCYTES.

Wilson and Chowning (1902a, p. 133; 1903a, p. 64) report a slight increase of leukocytes—from 12,000 to 13,000 (or 14,000; see 1903a, p. 50)—in 4 cases examined; further counts are given in 1904a, p. 39.

Anderson (1903a, p. 507; 1903c, p. 22) says that the white cells are increased in number, varying from 8,000 to 12,000, the most interesting feature being an increase in the large mononuclears, which in an average of 2 cases gave 11.4 per cent.

Polymorphonuclear leukocytes.....	77.7
Large mononuclear leukocytes.....	11.4
Small lymphocytes.....	10.0
Eosinophiles.....	.9

---

100.0

In case 11 (1904) the leukocytes ran up to 15,600 (Ashburn). It is a point of some interest that the increase in large mononuclears, as reported by Anderson, is in harmony with protozoan infection in so far that in malaria and kala-azar there is also an increase in large mononuclears, but in canine piroplasmiasis it is the polynuclears which are increased.

COMPARISONS.—For Texas fever Smith and Kilborne (1893, p. 50) say: "Any unusual increase in numbers was not noted in stained preparations of any case which came under observation. In some cases an abnormal crowding together of leukocytes was observed in dried preparations, which crowding must be regarded as having existed within the blood vessels, for there was no time for any massing together after the blood had left the vessels."

In canine piroplasmiasis there may be considerable leukocytosis, the number of leukocytes being increased 2, 3, or 4 times the normal, so that instead of having 7,000 to 8,000 (normal), as many as 40,000 may be counted; the multiplication almost entirely affects the polynuclear elements, this being especially marked in slow-running cases (Nuttall, 1904, p. 238).

#### HEMOGLOBIN

In 5 cases examined during various stages of the disease, the hemoglobin was 50 to 60 per cent: one child of 12 years, examined 2 months after convalescence, showed Hb. 80 per cent (Wilson and Chowning, 1902a, p. 133; 1903a, p. 64; 1904a, p. 40). Anderson (1903a, p. 507; 1903c, p. 22) reports a steady but never very rapid decrease in the percentage of hemoglobin, one case going as low as 50 per cent.

COMPARISON.—For canine piroplasmiasis (Nuttall, 1904, p. 238) there is a great fall in the percentage of hemoglobin, namely, to 13, 12, 6.4, or even to 3.5 per cent.

#### WIDAL TEST.

The Widal reaction with *Bacillus typhosus* is not present. (Wilson and Chowning, 1902a, p. 133; 1903a, p. 64; 1904a, p. 40; Anderson, 1903a, p. 507; 1903c, pp. 22, 33, 37.)

#### PARASITES.

See also page 19.

Freshly drawn blood from patients during their illness when examined with a one-twelfth oil immersion objective shows parasites sparingly in the red blood cells (Wilson and Chowning, 1902a, p. 133; 1903a, p. 64; 1904a, p. 40). Blood was examined from 3 recovered cases, 1 of 2 months, 1 of 1 year, and 1 of 2 years without finding the hematozoon (1903a, p. 64; 1904a, p. 40). Case 115, examined 14 days after patient had been discharged by physician, still showed parasites in the blood (1904a, p. 40).

Anderson (1903a, 1903c) also reports the parasites in the blood.

Ashburn and I have failed to confirm these observations: see pages 19.

COMPARISON.—It will be recalled that Wilson and Chowning state that in "spotted fever" probably not over 0.2 per cent of the red cells in the circulating blood are infected, but the parasites are more common in the spleen and in certain other portions of the body.

For Texas fever, Smith and Kilborne (1893, pp. 61-65) state that the numbers of infected corpuscles circulating in the blood during the high fever is usually quite small; 0.1 to 1 per cent would be a fair estimate in most cases. Toward the fatal termination there may be from 5 to 10 per cent of the corpuscles with the pyriform

parasites present. Larger numbers of parasites are found within corpuscles in the capillary blood of congested areas, as is seen by the following table of a case in which 2 to 3 per cent of the circulating corpuscles were infected before the cow was killed:

"In blood from skeletal muscles, very few infected corpuscles.

"In blood from the right heart, very few infected corpuscles.

"In blood from marrow of sixth rib, very few infected corpuscles.

"In blood from the left heart, 2 to 3 per cent infected corpuscles.

"In blood from lung tissue, 2 to 3 per cent infected corpuscles.

"In liver tissue, 10 to 20 per cent infected corpuscles.

"In kidney tissue, 10 to 20 per cent infected corpuscles.

"In hyperæmic fringes of omentum, 50 per cent infected corpuscles.

"In heart muscle, 50 per cent and many free parasites."—Smith and Kilborne, 1893, page 62.

In some cases the liver blood was infected to 40 or 50 per cent, and kidney blood to 80 or 90 per cent.

Starcovici reports for hemoglobinuria that 90 per cent of the corpuscles in the kidneys may show infection, but fewer infected corpuscles are found in the circulating blood. In carceag the blood in the spleen and in the hemorrhagic edema may be infected to 5 or 10 per cent. In the larger vessels scarcely 1 per cent.

For canine piroplasmosis, Nuttall (1904, p. 228) reports that the parasites occur in the blood throughout the body, being most numerous in the internal organs.

#### SPLEEN.

The spleen is uniformly enlarged and tender on palpation (Wilson and Chowning, 1902a, p. 133; 1903a, p. 64; 1904a, p. 40). It was 3 to 3½ times its normal weight; the capsule was distended and thinned; on section the tissue was found dark red and so soft as to be in most cases confluent; the outlines of the Malpighian bodies were obliterated; the omentum covering the spleen was usually congested (Wilson and Chowning, 1904a, p. 41). The spleen shows an engorgement with red blood cells and leukocytes; the outline of the Malpighian bodies are lost; there is a marked infiltration of leukocytes, mostly of the polynuclear type, in the region of the Malpighian bodies; there is much blood pigment, both free and within phagocytes; many piroplasmata are present, both free and within red cells, many of which have been taken up by phagocytes.

According to Anderson (1903c, p. 23), the spleen is enlarged early and may extend 1 or 2 inches below the costal margin; on post-mortem (1903c, p. 38) it is usually purple in color, soft, diffuent, and from 3 to 4 times its normal weight; the vessels are engorged with blood; many mononuclears are present containing from 1 to 4 red blood cells; there is no free pigment. In case 35 (1903c, p. 13) the spleen was much increased in size, and this was the only abnormal appearance at post-mortem; in case 121 (1903c, pp. 35-36) it was enlarged and easily palpable 1 inch below costal margin.

COMPARISON.—In Texas fever the grayish Malpighian bodies and the whitish trabeculae have all disappeared from view within the distended pulp; a microscopic examination shows that the enlargement and peculiar color of the spleen tissue is due to an engorgement with red blood corpuscles. With this engorgement there may be associated a variable number of large cells containing coarse granules and from 2 to 12 red corpuscles, or else the remains of these corpuscles in the form of irregular clumps of yellowish pigment. The pigment is also free in masses of variable size. Examination of fresh pulp from spleens of healthy cattle shows that the presence of large quantities of free pigment of the form described is not uncommon. (Smith and Kilborne, 1893, page 28.)

In carceag the follicles are usually indistinct and the spleen is hyperemic.

In hemoglobinuria of cattle the follicles are seldom distinct.

*Size.*—The size and weight of the spleen on post-mortem have been reported as follows:

7 ounces after 4 hours in paper, case No. 107, Wilson and Chowning, 1903a, page 48.

9 ounces, case No. 94, Wilson and Chowning, 1903a, page 58.

17 ounces, after 12 hours in paper, case No. 3, Wilson and Chowning, 1903a, page 54.

22 ounces, after 8 hours in paper, case No. 91, Wilson and Chowning, 1903a, page 53.

25 ounces, after 12 hours in paper, case No. 107, Wilson and Chowning, 1903a, page 48.

3 times normal weight, case No. 97, Wilson and Chowning, 1903a, page 56.

20 ounces, 1 hour after removal, case No. 120, Anderson, 1903c, page 33.

In cases of 1904, it was enlarged in Nos. 3, 7, 10, and 11; dullness was increased in case 5, but not obtainable in case 8.

*COMPARISON.*—The spleen is enlarged in Texas fever (very much enlarged, hence the name splenic fever), in hemoglobinuria in cattle, and in carceag in sheep, and is often 3 to 4 times natural size in canine piroplasmosis.

*Color.*—The spleen is reported as dark in cases 91, 94, 107, 120; very dark in cases 93, 97.

In 1904 the spleen of case No. 11 on post-mortem was of a slaty purple in color.

*COMPARISON.*—In Texas fever the spleen is reported as dark brownish-red, dark in hemoglobinuria of cattle; in canine piroplasmosis it is reported as "pale, bloodless, like other organs; scarcely stains paper when smeared thereon" (Robertson); Nuttall observed little change; in France it is dark.

*Capsule.*—The capsule of the spleen is reported as stretched and thin in cases 89, 91, 93, 107; it stripped easily in cases 94, 97.

*COMPARISON.*—In Texas fever the ordinarily rather thick whitish capsule is very much distended and attenuated, so that the dark pulp shows through it very distinctly.

*Pulp.*—The spleen pulp is reported as soft and diffuent in cases 89, 91, 93, 107, 120; almost fluid and deep red in case 97; decidedly diffuent, of deep yellowish-red color, in case 94.

In case 11 of 1904, the spleen was soft and easily torn.

*COMPARISON.*—In Texas fever the pulp may be firm or it may be partly diffuent, welling out as a semifluid mass from the incised retracting capsule. It is reported as soft in carceag and canine piroplasmosis (France).

*Adhesions.*—In case 93 (of 1902), the spleen was adherent to the gut. In case 11 of 1904, it was bound down by posterior adhesions, and adhesions to stomach.

In case 107 the portion of the omentum covering the spleen was darkened and apparently disintegrating; in case 89 it was dark, congested, and soft; in case 91 it was pale and apparently normal; in case 93 it did not differ from the omentum elsewhere (Wilson and Chowning, 1903a, pp. 48, 51, 54).

#### TEMPERATURE.

#### CHILL.

*Idaho.*—During the first week following the malaise the patient complains of chilly feelings (Bowers, 1896, p. 63). Some cases begin with a severe chill, and others with more or less chilly shudderings frequently referred to the spinal region; still



others with little or no chill (Collister, 1896, p. 63). The disease is sometimes ushered in by a chill (Fairchild, 1896, p. 62). Figgins (1896, p. 64) states that the attack begins with a chill. According to Springer (1896, p. 61), the chill follows the malaise. Maxey (1899, p. 435) states that the patient feels flashes of heat and cold, but no marked chill.

*Montana.*—The attack comes on by either a well-marked chill or by chilliness, simultaneous with fever; the chilliness, although most severe at the onset often continues more or less throughout the attack, coming on at intervals, generally mornings, and becoming lighter day after day until within a week or so it seems but little more than chilliness from light covering (Gwinn, 1902). According to McCullough (1902, p. 226), the onset may be marked by a sudden and severe chill or by slight chilly sensations, mostly in the morning. Wilson and Chowning (1902a, p. 132; 1903a, p. 61; 1904a, p. 37) report that the malaise is followed by a well-marked chill, which is usually most severe at the beginning and recurs at irregular intervals, though with decreasing severity. Anderson (1903a, p. 507; 1903c, p. 21) states that for a few days the patient may have chilly sensations, and finally there is a well-marked chill; he reports cases as follows:

Case 97 began with chills and vomiting, and with a rapid rise in temperature (pp. 16-17).

Case 115 was bitten by ticks April 1; complained of being chilly on April 7 or 8 (p. 24).

Case 116 was bitten by tick April 13; severe chill on April 19 (p. 26),

Case 117 was bitten by tick April 16; marked chill on April 20 (p. 27).

Case 118 was bitten by tick; chill April 20 (p. 27).

Case 120 found tick bites April 28; had chill same day (p. 29).

Gates (1903, p. 48) reports for one patient a hard chill during the last of the 1st week; he (1905, pp. 111-112) also reports chill for cases 11 and 14, in the latter case 10 days after the bite; later the chill recurred; pronounced chill for case 16.

During the 1904 season, chills occurred in cases 2, 3, 5, 6, 8, and 9.

COMPARISON.—Chills are reported for carceag.

#### FEVER.

*Idaho.*—During the first week following the incubation, the patient takes to bed with a temperature of 102° to 105° F., pulse 90 to 120; in favorable cases and in those of moderate severity there is a gradual decline in fever during the second week; the temperature varies in different cases; there is a daily rise during the first 4 or 5 days; the evening temperature is about 1° to 1½° higher than the morning remission; a temperature of 102½° to 104° is not uncommon by the fourth or fifth day; having reached its acme, the fever persists for several days; at the end of the second and during the third week the fever falls by lysis to an evening record of 98.4° (Bowers, 1896, p. 63). According to Collister (1896, p. 63) the febrile stage gradually follows the chill; it continues 2 or 3 weeks; it is not common to find a temperature over 103°, except in occasional cases. Fairchild (1896) states that in some cases febrile action runs high; it usually ranges from 101° to 104½° or 105°, and is continuous, showing but slight remissions. Figgins (1896, p. 64) reports the fever as remittent; the temperature ranges from 100° to 105°; pulse, 100 to 120. Springer (1896, p. 61, 62) says that after the chill the fever sets in, ranging from 103° to 105°; the fever ranges high and continues from 10 to 14 days; then it intermits for the following week or two. Zipf (1896, p. 65) says that the usually sudden onset is accompanied by high fever; the fever is continuous, lasting one to two weeks and is out of proportion to the danger of the disease; it also leaves the patient weak for weeks. Maxey (1899, p. 435) describes the fever as of the continuous type, beginning on the first day and rising gradual'y until it reaches 102° to 103° on the third or fourth day, when the eruption

usually appears; it is highest on the fourth to seventh day, corresponding to the period of most profuse eruption; there is a difference of  $1^{\circ}$  to  $1.5^{\circ}$  F. between the minimum morning and maximum evening temperature, which difference is maintained until about the tenth to fifteenth day, when the temperature line becomes erratic, for at this time it is apt to take sudden jumps up and then as suddenly down, while at the same time the average temperature is gradually going down, until by the end of the third week the patient is entirely free from fever. The Medical Sentinel (1899, p. 457), speaking editorially, refers to the fever as remittent in type.

*Montana.*—The fever comes on with or rapidly follows the initiative chill, so that upon the first visit the temperature is usually  $102^{\circ}$  to  $104^{\circ}$  F.; it becomes gradually higher day after day until it reaches its maximum in 2 to 7 days, when it ordinarily registers  $103^{\circ}$  to  $106^{\circ}$ ; there seems to be a slight evening rise above that of mornings; in probably all cases except the mildest, one may be misled in the latter days of the attack in thinking the fever abated upon feeling the skin, or by the thermometer registered in the axilla, while the rectal temperature shows to the contrary; this difference in temperature is apparently caused by the slow, feeble, obstructed circulation, the exterior and the extremities becoming cool from a lack of blood supply; in cases where recovery takes place, the fever begins to abate about the fourteenth day and gradually recedes until it disappears, on an average, on the twenty-first day; 2 cases had subnormal temperature mornings and about  $1^{\circ}$  of fever at 6 p. m. almost during the entire attack. (Gwinn, 1902.)

McCullough (1902, p. 226) says that the temperature and pulse assume the form of most continued fevers, both gradually increasing, until the acme of the disease is reached in nonfatal cases about the end of the second week; very high temperature is not usual, ranging from  $102^{\circ}$  to  $106^{\circ}$ .

According to Wilson and Chowning (1902a, p. 132; 1903a, p. 62; 1904a, p. 37) after the initial chill, fever rapidly develops, and may reach  $103^{\circ}$  to  $104^{\circ}$  F. on the second day; it gradually increases and reaches its maximum in from 5 to 7 days, when it may register  $105^{\circ}$  to  $107^{\circ}$  F. (rectal temperature); the difference between rectal and axillary temperature is sometimes as much as  $2^{\circ}$  F.; usually a slight evening increase and morning decrease are noted; the temperature occasionally becomes normal or subnormal 18 to 24 hours before death; when recovery occurs, it is by lysis, much as in typhoid; the diminution of the fever begins about the end of the second week and reaches normal about 2 weeks later.

Anderson (1903a, p. 507; 1903c, p. 21) states that before the distinct chill there is little or no fever in the morning, with a slight rise in the afternoon; after the chill there is an abrupt rise, and from then on the fever gradually rises in the evening, with a slight morning remission. The maximum is usually reached on the eighth to the twelfth day; then, in a favorable case it gradually falls, becoming normal about the fourteenth to the eighteenth day, usually going to subnormal for a few days; in fatal cases the fever remains high, from  $104^{\circ}$  to  $105^{\circ}$  or  $106^{\circ}$  F., and the morning remissions are very slight or not present.

Gates (1903, pp. 48, 49) reports the temperature for two cases; in one case the patient was given small doses of aconite and spirit of nitrous ether and small doses of alcohol until the fever was reduced and bowels moved freely; the patient was sponged with cool and cold water, as needed for high temperature; the fever ran an irregular course, with great variation, reaching at times a temperature  $104.5^{\circ}$  F., and again sinking to  $97^{\circ}$  F. This low temperature was observed during the last of the first week of the disease, at which time the patient was in a state of collapse, being almost pulseless and having a hard chill at the time.

COMPARISONS.—In Texas fever, if the temperature of exposed animals be taken once daily—say, in the morning—it will be found that at the onset of the disease it will rise within 24 hours from the normal to  $104^{\circ}$  F. or even higher. In the following 24 hours it may rise to  $105^{\circ}$  or  $107^{\circ}$  F. The continued daily record will then

show a high temperature until the disease terminates fatally or in recovery. In the former case it may fall from 2° to 4° below the normal just before death. When recovery ensues, it falls as quickly to or even below the normal as it rose in the beginning of the attack. If the temperature be taken twice daily—in the morning and the evening—a new set of phenomena appear. The temperature at the outset rises during the day, is highest in the evening, and may be low again in the morning. This oscillation, partly a normal occurrence, may be noticed for 3 or 4 days in some cases, the morning temperature gradually rising until it is as high as the evening temperature. The high temperature then remains continuous until the end of the fever. (Smith and Kilborne, 1893, p. 16.)

For canine piroplasmosis, Nuttall (1904, pp. 232-233) reports:

“South Africa: Fever recorded in all cases, and may be present when the dog appears well, thus constituting usually the first symptom. Fever starts at 104.2° to 105.4°, and oscillates or rises to 105° or 106.6°, even 107° F. In chronic cases (Chart V) there may be great oscillations in temperature, which may fall below normal (97° to 98° F., about 36° C.) and again rise. Toward death the rectal temperature gradually falls far below normal; in three of my dogs 98.2°, 97.2°, 90° F. (32.2° C.) were recorded, respectively, when last taken.

“France: In acute cases fever at onset may exceed 40° C. (104° F.), is maintained usually 2 to 3 days, then the temperature falls below normal, even down to 33° C. (91.4° F.). Rarely temperature is seen to oscillate, then gradually fall. In young dogs, which die very quickly, initial fever may be absent, parasites appear in the blood, and temperature sinks until death.

“In chronic cases fever usually absent; slight when present; rarely exceeds 40° C. (104° F.). May be overlooked; lasts 36 to 48 hours, then falls. In one case a ‘quartan fever,’ with remissions, as in the human malaria, observed.”

#### RESPIRATORY SYSTEM.

##### BRONCHITIS; COUGH.

*Idaho.*—There is considerable bronchial irritation, cough lasting during convalescence or as long as there is any appearance of the eruption (Figgins, 1896, p. 64). Fairchild (1896) agrees that a slight cough accompanies the disease. According to Maxey (1899, p. 435) there is occasionally some bronchial cough, which may or may not be accompanied by some pain in the lungs.

*Montana.*—An irritative cough generally exists from the first, but not to an extent to be especially noticeable (Gwinn, 1902). Wilson and Chowning (1902a, p. 132; 1903a, p. 62; 1904a, p. 37) state that a bronchial cough is frequently present at the onset. Anderson (1903a, p. 507; 1903c, p. 21) refers to a slight bronchitis after a few days; always present in the second week (1903c, p. 23). Gates (1905, pp. 111-113) reports cough for his cases, Nos. 11 (tenth day, especially well-marked symptom), 14, 15 (most troublesome), 16 (some, but not so much as usual).

In the 1904 cases no cough was recorded for cases 7, 9, and 13; in case 3 there was no cough on May 10, but the patient coughed freely on May 14; there was some cough in case 10.

*Bronchial glands.*—In case 11 (1904) the bronchial glands were found enlarged at autopsy.

##### THYMUS.

In case 11 (1904) remnants of the thymus were seen upon removal of the sternum.



Respiration is notably deeper, fuller, and more labored from the first than in health, as well as increased in frequency; the respiratory acts are labored and increased in frequency in proportion to the amount of cyanosis rather than the amount of fever. (Gwinn, 1902.)

According to Wilson and Chowning (1902a, p. 133; 1903a, pp. 64-65; 1904a, p. 40) the respiratory rate sometimes reaches 60 per minute in the adult, though ordinarily it does not run above 36 per minute; like the pulse rate, it is frequently out of all proportion to the temperature; it is regular, but usually shallow; it may be labored and accompanied by rattling, due to accumulation of mucus in the upper air passages, during the last day or two of life; Cheyne-Stokes respiration has not been observed.

Anderson (1903a, p. 507; 1903c, p. 23) states that the respiratory rate is always increased, usually varying from 26 to 40 per minute, in some cases reaching 50 to 60; it is regular, but often shallow. He reports hurried respiration for case 37 (Howard's case, p. 12), between 40 and 50 for case 56 (Howard's case, p. 14), 24 for case 90 (Brice's case, p. 16) the second day after onset, 32, two days after onset, increasing gradually to 45, for case 97 (Burton's case), taking his data from Wilson and Chowning, 1903a. In case 117 (p. 27) the respiration was at first normal, became more rapid and labored until a few hours before death, then gradually weaker; 26 and 28 for case 118 (p. 28).

Gates (1903, p. 50) reports in one case that the respiration varied from 30 to 40 throughout the course of the disease and continued until after all signs of heart action had ceased. He (1905, p. 113) reports Cheyne-Stokes respiration during last of second week in his case 16.

In the cases of 1904 respiration became poor (7) in case 2, the patient at times struggling for breath on May 8; Buckley observed Cheyne-Stokes respiration in this case. In case 3 it was slightly harsh and prolonged anteriorly; it became slightly stertorous on May 12; on May 13 the lung sounds were very harsh all over the front and back, with large coarse rales; the lungs were rapidly filling with fluid; for 5 or 10 minutes respiration would be quiet and regular, then very rapid (60) for a time; on May 14 the filling of the lungs progressed rapidly, edema well marked; on May 15 there was much noise in breathing. In case 5 the respiration suddenly ceased on May 21; artificial respiration was resorted to and in 5 minutes the patient breathed, was roused, and quite rational; failure of respiration continued to occur at intervals, patient apparently forgetting to breathe; hypodermics of morphine acted as a respiratory stimulant (Mills). In case 7 respiration became harsh, especially on right side. In case 11 respiration was depressed, falling on June 24 to 8 (patient receiving large doses of morphine).

Edema of lungs developed in case 2.

COMPARISONS.—For Texas fever, see above, page 63.

In canine piroplasmiasis breathing is accelerated, subsequently labored, irregular, and finally very shallow; in acute cases respirations are 36 to 48 per minute (accelerated), labored, gasping, and at times, especially in young dogs, accompanied by whining sounds; examination of thorax negative.



No adhesions were reported in cases 107, 89, 91, and 120. In case 93 the pleura was intensely adherent over entire surface of both lungs; the adhesions were very thick and fibrous; there was a history of pleurisy several years before. (Wilson and Chowning, 1903a, pp. 47, 51, 52, 54; Anderson, 1903c, p. 33.)

In 1904 the pleural cavities of case 11 were normal except a few adhesions between left lung and pericardium.

COMPARISONS.—In canine piroplasmosis, the peritoneal and thoracic cavities may contain fluid (Hutcheon); sometimes there is brownish serous exudate in thorax; in Lounsbury's chronic case there were pericarditis and pyothorax.

## LUNGS.

See also Gangrene; page 50.

Wilson and Chowning (1904a, pp. 41, 42) report hypostatic congestion; all the lungs show considerable congestion and swelling of the capillaries; many red blood cells containing parasites are present; in most cases many phagocytes are found which have taken up infected red cells and pigment granules; in one case there was considerable broncho-pneumonia; pleura was normal.

Anderson (1903c, pp. 33, 38) reports that the pleuræ are normal and do not contain excess of fluid; lungs show hypostatic congestion, occasionally pneumonia; in case 120 there were no consolidated areas, except a few points resembling emboli.

See also Complications, page 87.

Upon autopsy, the lung tissue in case 93 was fully crepitant; there was slight hypostatic congestion on both sides; in cases 89 and 91 both lungs were normal, except hypostasis on both sides; in case 107, the lungs were apparently normal, no pneumonia (Wilson and Chowning, 1903a, pp. 47, 51, 52, 54). In case 120, the lungs were normally inflated, no consolidated areas, except a few points resembling emboli (Anderson, 1903c, p. 33).

During the season of 1904, case 2 died of edema of the lungs; in case 3 also edema of the lungs developed; in case 8, slight edema of the lungs developed; there was edema of the right lung May 29, and on May 30 both lungs were edematous. In case 11, on autopsy, the right lung was lead color on upper surface, very dark posteriorly; several dark spots one-eighth inch in diameter anteriorly, but apparently old; entire lung edematous; posterior portion extremely congested, in a condition of hypostatic pneumonia, and sinks in water; left lung shows same appearance as right, except pneumonic area is less marked and less extensive.

COMPARISON.—In Texas fever the lungs are, as a rule, healthy; there is, in many cases, pulmonary edema, with or without emphysema, noticeable after death; in a few instances foci of dark red hepatization were observed in one of the principal lobes, which involved one or several lobules. (Smith and Kilborne, 1893, p. 26.)

In canine piroplasmosis the lungs are rarely affected (Hutcheon); Nuttall noted edema and pinkish frothy fluid in the bronchi and trachea; in France apoplectiform foci have been found; in young dogs dying quickly, usually there are acute edema and reddish foamy secretion in bronchi and trachea.

Hypostatic lobar pneumonia herds have been recorded in carceag.

## MUSCULAR SYSTEM.

See also Pains, page 76.

Gwinn (1902) reports rigidity of muscles of neck and back in one case. Several authors refer to the soreness and stiffness of the muscles.

Anderson (1903c, p. 23) says that the soreness of the muscles and bones causes the patient to change position often; muscular soreness is often very severe even in mild cases and lasts until recovery.

Wilson and Chowning (1903a, p. 47) report some tenderness on pressure along the spine (case 107), especially in the dorsal region, though this may have been due in part to the general soreness of the muscles.

In case 11 (1904) the muscles were well developed and of good color.

COMPARISON.—In Texas fever the lean meat may be of a brownish mahogany color and possess a peculiar sickening odor, or it may be normal in color or perhaps a trifle paler. In carceag the muscles are reported as pale and flabby.

## EMACIATION.

See also Fat, page 52.

Emaciation has not been reported in connection with "spotted fever," but it seems to be quite a prominent symptom in some piroplasmatic diseases.

Thus, for Texas fever, Smith and Kilborne report that there may be extreme emaciation during the period following the fever. For canine piroplasmosis, Nuttall (1904, pp. 231, 326) reports that there is a loss of weight which is greatly increased during the final stages, and appears to be more marked in long-continued cases; there is great emaciation.

## NERVOUS SYSTEM.

See also Pains, page 76; Photophobia, page 52; Extremities, page 55.

*Idaho*.—All cases are very nervous, sleepless, and throughout the disease suffer intensely; there is a hyperemic condition of the nervous system, as is shown by the general neuralgic pains; in my opinion it is a hybrid between typhoid fever and cerebrospinal fever, the disease having many symptoms common to both (Fairchild, 1896). Springer (1896, p. 62) says that the patients are usually very nervous and irritable. Sweet (1896) reports that the nervous system is sometimes involved; in such cases there is marked hyperpyrexia.

*Montana*.—McCullough (1902, p. 227) reports indifference to surroundings. According to Wilson and Chowning (1902a, pp. 132-133; 1903a, p. 63; 1904a, pp. 38), aside from the headache at the beginning, many patients show no nervous symptoms until just prior to death; a low muttering delirium, as in typhoid, is present in some severe cases, the patient being but partly rational; in the severe stages, picking at mouth, ears, and bed clothing is present; except at the onset the disease is remarkable for its freedom from pain.

Gates (1903, p. 50) reports for one case that there seemed to be a profound impression on the nervous system from the very first symptoms of the disease; muttering delirium and a semicomatose condition, from which the patient could be aroused only with much effort, were early and prominent symptoms. Later he (1905, p. 113) states in regard to his case 16 (1904) that the intensity with which the disease attacked the nervous system was marked from the onset; a low muttering delirium came on during the first week; during the second week the patient was in a heavy stupor from which she could be aroused with difficulty, but when aroused she would answer questions correctly and then, perhaps, talk at random; the condition of the mind approached normal during the third week.

During the season of 1904 nervous symptoms were prominent.

In case 2 hyperesthesia (see above, p. 51) was extreme, the weight of a palpating hand or even of the bed clothing caused extreme pain. For case 4 severe intracranial and supraorbital neuralgia, May 12, was reported; condition improved under codeine; in general the nervousness of the patient was marked in this case, as also in case 5. In case 6, who was of a neurotic temperament, the nervous symptoms were prominent, very marked, and constant; twitching of muscles, etc. On May 19, when touched anywhere on the body the patient was thrown into a state of tonus. In case 7 nervous disturbance was important and marked throughout illness. The patient thrashed around in bed, rolling head and throwing the arms around. He could not be made to lie on the left side for a minute at a time, but would immediately throw himself upon his right side or his back. In case 8 nervousness increased May 24; dullness increased with slight delirium; May 25 hyperesthesia was very marked; there was high nervous tension, the muscles of the back and limbs became very rigid; all nervous symptoms increased May 26, 27, and 28; a drink of water would produce spasm of pharynx and diaphragm; reflex excitability was so intense for 24 hours before death that a slight touch used in putting a spoon to the mouth, or sponging, etc., would cause spasm and rigidity of entire body. In case 11 the severity of the nervous symptoms pointed strongly to cerebrospinal meningitis. In case 13 there was picking at the bed clothing, muttering, and restless rolling from side to side.

#### MALAISE.

*Idaho.*—During incubation there is a feeling of lassitude and inaptitude for work (Bowers, 1896, p. 63). Many cases are taken suddenly without previous malaise (Collister, 1896, p. 63). Lassitude is mentioned by Dubois (1896, p. 64). Fairchild (1896, p. 62) says there are usually 2 or 3 days of malaise. Springer (1896, p. 61) states that there is a feeling of malaise for a few days preceding the chill, and Maxey (1899, p. 435) reports that the patient first notices a general malaise.

*Montana.*—In a few cases the disease seems to be preceded by a prodromal period of malaise for a few days (Gwinn, 1902). According to McCullough (1902, p. 226) the attack may come on insidiously with a feeling of malaise for a few days, gradually growing worse and merging into a well-defined "bone ache."

Wilson and Chowning (1902a, p. 132; 1903a, p. 61) and Anderson (1903a, p. 507; 1903c, p. 21) agree that many cases are preceded by a short period of malaise.

In 1904 case 3 complained of slight malaise on May 10; on May 12 this case showed stupor.

#### RESTLESSNESS AND INSOMNIA.

*Idaho.*—Sleeplessness is common during the first week (Bowers, 1896, p. 64). On account of the fever and the soreness and the pains in the extremities and back the patient rolls and tosses in a restless effort to find a comfortable position (Maxey, 1899, p. 435).

*Montana.*—There is considerable restlessness (Wilson and Chowning, 1902a, p. 132; 1903a, p. 62; 1904a, p. 37). Anderson (1903c, p. 23) says that the soreness of the



muscles and bones causes the patient to change position often; he reports (pp. 14, 15) marked jactitation for cases 56 and 57, and says (p. 28) that restlessness in case 118 was allayed by darkening the room.

Gates (1905, p. 111) reports insomnia as especially well marked in his case No. 11, persistent in case 14, not troublesome in case 15.

In 1904 all cases were reported as very restless, especially cases 2, 6, 7, and 11. Case 2 was markedly drowsy on May 4.

#### DIZZINESS.

McCullough (1902, p. 226) reports dizziness among the initial symptoms. This was not complained of in cases 1 to 11 (1904).

#### HEADACHE.

*Idaho*.—Cephalalgia is the most common and persistent symptom in the development of this disease; the pain is intense and persists without intermission; it is referred to the frontal region or to the occiput, or to the entire head (Bowers, 1896, p. 64). Collister (1896, p. 63) states that there is generally a severe headache. According to Dubois (1896, p. 64) the patient may be stricken down without warning with a severe frontal headache. Severe headache, particularly in the back part of the head, is mentioned by Fairchild (1896, p. 62) as an early symptom. Sweet (1896) also mentions headache. Violent headache is recorded by Zipf (1896, p. 65) as an initial symptom. On the second day the pain in the head becomes quite severe (Maxey, 1899, p. 435).

*Montana*.—There is a general aching and soreness of the whole body (Gwinn, 1902). According to Wilson and Chowning (1902a, p. 132; 1903a, p. 62; 1904a, p. 37) the headache may be severe at the onset. Anderson (1903a, p. 507; 1903c, p. 21) reports some pain in the head; he gives (1903c, pp. 24, 27) headache as following the tick bites in case 115 and as present in case 118. Gates (1905, pp. 111-113) reports for his cases 11 and 16 severe headache; for case 11, frontal headache following the chill.

Headache was present, to a greater or less degree, in cases 1 to 11 during 1904. In case 1 it was reported as frontal; in case 5 it began at the time of the chill; in case 8 it was very severe; in case 11 it was both frontal and occipital.

#### PAIN, OTHER THAN HEADACHE.

*Idaho*.—During the first week following the incubation period there is pain in the back and legs and a muscular soreness over the entire body; it is severe in the lumbar region or along the entire spine and in the lower extremities (Bower, 1896, pp. 63, 64). Collister (1896, p. 63) states that there is pain of a rheumatic character in the back and limbs, mostly referred to the joints. Dubois (1896, p. 64) mentions intensely severe pains in joints and muscles as an early symptom; this pain "is boring, breaking, and stabbing, and appears to penetrate into the very substance of the bones." Fairchild (1896, p. 62) reports shooting pains throughout the body and limbs, usually more severe in the bowels and back; it is neuralgic in type and is controlled only by morphine; the pain may appear early, and continues throughout the attack. Figgins (1896, p. 64) records pains in the extremities, and muscular soreness. According to Springer (1896, p. 62) the patient usually complains of severe pains throughout the body, especially in the back and stomach, and in many cases in the larger joints; these pains are not continuous, but are of a shooting character and cause the patient to cry out on any movement. Sweet (1896, p. 61) says that the onset is usually accompanied by severe breakbone pains; the intense



boneache is suggestive of dengue. Zipf (1896, p. 65) reports backache. According to Maxey (1899, p. 435) the bones and muscles soon begin to ache, and on the second day the patient feels sick enough to take to his bed; he already feels very weak and depressed, and the pains in the back and in the joints and muscles of the extremities are becoming quite severe; accompanying the bronchial cough there may or may not be some pain in the lungs.

*Montana.*—At the onset there may be intense soreness seemingly of the entire muscles of the body (McCullough, 1902, p. 226). According to Gwinn (1902) there may be general aching and soreness of the whole body. Patients while conscious usually complain most bitterly of general aching and soreness, and prefer to be moved as little as possible, especially after the disease has progressed a few days. Sometimes the pain is referred to as being more in the head, in other cases the back, while in others it does not seem to predominate at any single point. Wilson and Chowning (1902a, p. 132; 1903a, p. 62; 1904a, p. 37) state that the onset is accompanied by a severe aching in the bones and muscles, with pain in the back and joints. The patient is usually very weak (1903a, p. 45). In case 109 there was no stiffness of the neck or back, though some pain was present on pressure over the spinal processes of the vertebræ, especially those in the dorso-lumbar region. They also report (1904a, p. 37) that cases Nos. 94, 96, 97, 115, 116, 117, 119, and 120 give a history of soreness about the tick bite, and pains radiating therefrom which continued until the initial chill, but (1902a, p. 133; 1903a, p. 63; 1904a, p. 38) except at the onset the disease is remarkable for its freedom from pain. Anderson (1903a, p. 507; 1903c, p. 21) reports for the onset some pain in the back and head and soreness of the muscles and bones. He states (1903c, pp. 21, 23) that the pain in the head and back is usually severe during the first week, while the soreness of the limbs causes a sensation as if the limbs were in a vise, and causes the patient to change position frequently. The soreness of the muscles is often very severe in mild cases and lasts until recovery. Anderson (1903c, p. 16) records pains in head, back, and upper and lower limbs and soreness of muscles in all parts of the body for case 90; (p. 26) case 116 was bitten by tick under the arm on April 13, and the chill on April 19 was followed by aching pains; the wound and axillary glands were sore and swollen on April 13, soreness was less marked after a few days, but still present; it became much worse on April 19, with shooting pains radiating from the axilla, through the shoulder, down the arm and side of the body; aching pains in the back followed the severe chill and extended over the whole body; (p. 27) case 118 complained of aching pains in the back and limbs; (p. 29) case 119 experienced soreness from the wound made by the tick bite; pain and swelling was present, extending down the side of the head behind the ear to right side of neck; (p. 29) case 120 had pain in back and limbs on day preceding removal of ticks, the pains continued the next day; (p. 36) case 121 had pain in bones and joints, and (pp. 34, 37) backache on May 10, severe pain in back and limbs on May 14, backache and soreness of muscles of legs and arms on May 17, no pain in head or back on May 23. Anderson (1903c, p. 40) advises Dover's powders or morphine sulphate to relieve the pain. Gates (1905, pp. 111-113) states that in his case 11 the headache was followed by severe aching of all of the skeletal muscles, especially severe in the calves of the legs; case 14 complained of pains in the tibiæ, intense backache, pains in ankles and knee joints, and great muscular soreness, including muscles of eye; case 15 complained of general muscular soreness, severe headache and backache, and great exhaustion; case 16 complained of aching in limbs and back.

In 1904, case 1 complained of "general body aching;" case 2 had some pain in back and head, and complained of general soreness after appearance of the eruption; case 3 complained of backache; case 4 complained of suprascapular and lumbar pains, and later of pains in

the head; case 6 complained of headache, backache, and legache, and general aching and pain; case 7 complained only of headache, pain in the abdomen and back of the neck; later (June 8) pain in the neck disappeared, but on June 9, and on June 15, patient complained of pain in the knees; case 11 complained especially of pains in the neck and lumbar region; case 12 complained of great soreness all over the body, the feet were exquisitely tender, and continued so until he left the hospital.

## MIND.

*Idaho.*—The mental processes become dulled and the patient is listless and apathetic (Bowers, 1896, p. 64).

*Montana.*—In all attacks attaining a marked degree of severity the patient's mind is affected, first noticeable from incoherent and rambling speech when the temperature happens to be high, and if the case be dangerous in severity the disturbed thought sooner or later merges into delirium, usually followed by coma and death (Gwinn, 1902).

According to Anderson (1903a, p. 507; 1903c, p. 23) the mind is usually clear, even in severe cases, until within a few hours of the end (see cases 89, 116-121).

Case 7 (1904) was reported as answering questions intelligently up to within a few hours of death. Illusions were reported for case 4 on May 13; on 15th, illusions, weariness, and sleeplessness; illusions disappeared on May 19; case 3 showed stupor on May 12.

## DELIRIUM.

*Idaho.*—Delirium occurs in severe cases; it is of a typhoid character, and due to fever or to toxemia (Bowers, 1896, p. 64).

*Montana.*—See also Mind, page 78.

According to McCullough (1902, p. 226) delirium usually manifests a very active part in the symptoms, and may be low and muttering, or only a mental hebitude, the patient being partially rational. Anderson (1903c, p. 12) reports marked delirium for case 36 (Buckley's case, 1897); case 74 (Putney's case, 1900) showed delirium about the fourth day (p. 14); case 102 (McGrath's case, 1902) was delirious much of the time after the fourth day (p. 11). Gates (1903, pp. 48, 50) records slight delirium in one case; in another case a muttering delirium and a semicomatose condition were among the early and prominent symptoms. Later (1905, pp. 115) he reports that the delirium in his case No. 7 (1901) lasted for two weeks.

In 1904 case 1 presented delirium, which soon passed to coma; delirium was present in cases 2, 3, and 6; in case 9 the mind wandered and passed to delirium; in case 11 the delirium was at times violent; case 12 showed delirium at no time, but case 13 was delirious.

## COMA.

Coma and death usually follow the delirium (Gwinn, 1902). According to Anderson (1903a, p. 507; 1903c, p. 23), quoted from Wilson and Chowning (1903a), case 37 (Howard's case, 1898) was entirely comatosed for 3 days; case 8 (Gwinn's case, 1899) showed a semicomatose condition as an early symptom; case 118 (1903c, p. 28) passed into a state of semiconsciousness, gradually increasing to total unconsciousness, which gradually passed away, having lasted 72 hours. Gates (1903,

p. 50) reports a patient in a semicomatose condition, from which he could be aroused only with much effort (early symptom). Case 6 (1900) was in a very deep stupor for 10 days prior to death (Gates, 1905, p. 115).

In 1904, coma in case 1 followed the delirium and lasted till death; coma was also present in case 2 for some hours before death; case 3 was marked by the sudden onset and prolonged duration of coma; in case 6 coma preceded death a few hours; in case 8 coma was present to some extent May 26, and almost complete coma was reported May 27.

#### CONVULSIONS.

Case 95, a child of 2 years, had convulsions (Wilson and Chowning, 1903a, p. 60).

In 1904, case 7 showed convulsions about 8 hours before death, and there was almost a state of convulsion in case 6.

#### OPISTHOTONOS.

*Idaho.*—"In one case I found marked opisthotonos during the fourth week of the disease, which proved fatal. In this case there were marked cerebral conditions." (Fairchild, 1896.)

*Montana.*—Gwinn (1902) in one case observed rigidity of the muscles of the neck and back, very much resembling that of cerebrospinal meningitis. Wilson and Chowning (1902a, p. 133; 1903a, pp. 50, 57; 1904a, p. 38) and Anderson (1903c, p. 23) state that there is no opisthotonos.

In 1904, cases 2 and 3 presented toward death a tendency to opisthotonos, but the patients had received strychnine. Two unpublished cases of 1902 were described to me (not by a physician) as presenting marked opisthotonos. In Howard's case 7 there was slight opisthotonos reported during the convulsions.

#### BRAIN AND SPINAL CORD.

In one autopsy, Gwinn (1902) has been told, there was found a serous fluid in the fourth ventricle of the brain.

There is a slight congestion of the capillaries of the meninges; a few vessels of the cortex contain infected red blood cells; there is some distention of the pericellular spaces in the cortex; little or no chromatolysis is shown by Nissl's stain (Wilson and Chowning, 1904a, p. 43). The meninges of the brain and spinal cord showed a slight congestion, apparently hypostatic; there was no basilar (or other) meningitis (Wilson and Chowning, 1904a, p. 42). The vessels are somewhat congested in the spinal cord, as in the brain, and contain a small number of infected corpuscles; in one case the anterior horn cells show considerable chromatolysis with Nissl's stain; no fiber degeneration is shown by Weigert's stain (Wilson and Chowning, 1904a, p. 43).

Upon autopsy the brain substance was normal in color and consistency in cases 91 and 107; examination of the central nervous system in cases 89, 93, 94, and 97 was not permitted (Wilson and Chowning, 1903a, pp. 48, 52, 53, 55, 56, 58). Anderson (1903c, p. 33) makes no mention of the central nervous system of case 120.

In 1904, case 11, the veins on the surface of the brain were distended with blood; no pus nor lymph was found at base of skull; ventricles



appeared normal, except for distention of veins; a small amount of bloody serum was found in one lateral ventricle, the blood probably coming from a cut vein: on section the cerebrum appeared about normal; basal ganglia on section appeared normal; section of pons and cerebellum showed nothing abnormal.

The meninges over the occipital lobe of case 91 were congested (hypostatic), but otherwise normal; in case 107 the meninges were normal, except a slight congestion (hypostatic) in the vessels of the pia over the occipital lobe; there was no evidence of meningitis (Wilson and Chowning, 1903a, pp. 52, 48).

In case 11 (1904) the dura showed outer surface injected, but otherwise normal; removal of dura showed some adhesions at the vertex between the membranes and the brain substance, the area of adhesions being small.

In case 91 there was no inflammation or marked congestion in either of the meninges of medulla and cord; in case 107 there was no inflammation of the upper 6 inches of medulla and cord (Wilson and Chowning, 1903a, pp. 48-49, 55).

In case 11 (1904) section of the medulla showed nothing abnormal; the spinal cord showed considerable injection of the vessels, probably hypostatic; no lymph exudation or other evidence of inflammation was present: dura was normal; cross sections of cord at 1-inch intervals showed nothing abnormal; 15 cc. of clear spinal fluid was aspirated through the lumbar region before the canal was cut open.

Doctor Alton says that case 13 may possibly have been a case of meningeal irritation following measles, or may have been due to tick bite and infection from that source (no autopsy).

Local physicians have repeatedly spoken of the resemblance of "spotted fever" to cerebrospinal meningitis, and, in fact, the resemblance in some cases is very striking. Although the central nervous system has been examined upon autopsy in only a few cases, still it would seem rather remarkable that none of these autopsies showed the pathological lesions in case this disease were actually meningitis. At present, therefore, we are not justified in concluding that the "spotted fever" under discussion is cerebrospinal meningitis.

COMPARISON.—In Texas fever no nervous lesions were found which can be regarded in any sense as peculiar to or characteristic of the disease. It may be said, in general, that the brain shared the general tendency toward the injection of the capillary system. The vessels of the pia and the plexuses were engorged, and over the frontal lobes and near the great transverse fissure it was more or less pigmented—a condition also met with in other diseases. The gray matter of the cerebrum and especially of the cerebellum appeared of a more pinkish color. The white substance was normal in color, the ventricles free from fluid (Smith and Kilborne, 1893, pp. 25-26).

In canine piroplasmiasis a slight congestion of the meninges is found in some cases.

#### KERNIG'S SIGN.

Kernig's sign is absent (Wilson and Chowning, 1902a, p. 133; 1903a, pp. 49, 50, 57; 1904a, p. 38).



## URINARY SYSTEM.

## KIDNEYS.

*Idaho*.—Collister (1896, p. 63) states that the kidneys are often disturbed.

*Montana*.—Gates (1905, pp. 115) mentions severe parenchymatous inflammation for his case 10 (1903), and says that the kidneys suffered especially in case 12 (1903). Gwinn (1902) reports slight enlargement of the kidneys in one case on post-mortem. Referring to pathology Wilson and Chowning (1903a, p. 67; 1904a, p. 42) state that in all cases examined one or both kidneys showed small subcapsular hemorrhages on the ventral surface; the cortex on section was congested. Upon microscopic examination numerous phagocytes were found, each containing from 1 to 8 faintly outlined red blood cells, in nearly every one of which is a parasite; the kidney shows acute parenchymatous nephritis. Later (1904a, pp. 42, 43) they add that the capsule strips readily and there is some extravasation of red-blood cells, particularly in the cortex. Anderson (1903c, p. 38) summarizing autopsies on 7 cases (including the 6 autopsies reported by Wilson and Chowning, 1903a) states that the kidneys are enlarged; capsule usually not adherent; small subcapsular hemorrhages on ventral surface; on section, congested and swollen cortex; pyramids well outlined and deep red in color; small hemorrhages in pelvis; microscopically there are minute extravasations of blood in cortex and under the capsule; veins filled with blood; nuclei of convoluted tubules stain poorly; cells granular and in some places detached; newly formed casts in tubules; bladder normal and usually with small amount of dark urine.

In case 3 there were small subcapsular hemorrhages in both kidneys. In case 89 a small ecchymotic area was present immediately underneath the capsule on the anterior surface of the right kidney; the left kidney showed no ecchymotic areas, but otherwise was like the right kidney. In case 91 several minute hemorrhagic spots were present in the capsule over the ventral surface of each kidney. In case 94 the left kidney was normal in size and there was a hemorrhagic area near upper pole and on anterior surface; the right kidney was normal, except on section (see below). In case 97 the left kidney was about normal in size; the right kidney was small; fetal lobation was present. In case 107, 2 or 3 ecchymotic hemorrhages were present in the ventral portion of the capsule over the left kidney.—Wilson and Chowning, 1903c, pp. 48, 51, 53, 55, 56, 58. Anderson reports (1903c, p. 33) in reference to case 120 that the kidneys were enlarged; the left kidney weighed 10 ounces; there were minute subcapsular hemorrhages, especially over the greater curvature.

In case 11 (1904) the right kidney measured 12 by 7 cm.; the left kidney measured 13 by 7 by 6 cm., areas of distinct pallor were scattered over the surface.

In cases 89 and 94 the capsule stripped easily. In case 97 the capsule was adherent and slightly hemorrhagic in the left kidney, but the capsule stripped easily from the right kidney.—Wilson and Chowning, 1903a, pp. 51, 56, 58. Anderson (1903c, p. 33) reports the capsule as adherent on the left kidney in case 120.

In case 11 (1904) the capsules of both kidneys were adherent, carrying substance with them in removal.

In case 3 the cortex of both kidneys, on section, was slightly congested. In case 89 the section of the cortex appeared slightly congested. In case 91 the section of both kidneys was congested, but otherwise normal. In case 94 the cortex of the left kidney was normal in thickness, with hemorrhagic areas over the cut surface; the pelvis was normal; in the right kidney similar hemorrhagic areas were seen, but

to a less extent. In case 97 section of the left kidney showed slightly hemorrhagic areas, the cortex was normal in thickness; on section the cortex of the right kidney was thin and dark, and hemorrhagic areas were seen over the whole surface, extending down to the pelvis. In case 107 the cortex of both kidneys, on section, was found congested.—Wilson and Chowning, 1903a, pp. 48, 51, 53, 55, 56, 58. Anderson (1903c, p. 33) reports for case 120 that on section the cortex was congested, the pyramids well outlined, and small hemorrhages about 1 mm. in diameter were present in the pelvis.

In case 11 (1904) the section of the cortex of the left kidney showed little if any alteration; the cortex of the right kidney appeared somewhat pale and thickened to Ashburn and myself, but to Mills it appeared about normal.

COMPARISON.—In Texas fever, Smith and Kilborne (1893, pp. 31–32) report that “in a considerable number of cases a sero-sanguinolent condition of the connective tissue and fat about the kidneys is observed. In a few cases the ventral surface of the organ appeared like two large blood blotches. The portion of the abdominal wall upon which the dorsal surface of the kidneys rest is free from these effusions.

“The kidneys themselves, like the other organs affected by this disease, vary more or less in color, according to the severity and stage of the disease. In those cases which succumb early in the fever and in which the bladder is filled with port wine colored urine, the kidneys are enlarged and of a uniform dark brownish-red color throughout. The usual markings are pretty well effaced. When fresh sections are examined from different regions, the vascular system is found quite uniformly engorged and distended with red corpuscles. The section is likewise sprinkled over with very minute pigment particles. Sometimes irregular masses of red corpuscles, run together as it were, are met with in the vessels of the pyramids. Lesions of the secreting structures are not discoverable. Hemorrhages are uncommon. In those cases which succumb after the hæmoglobinuria and the fever have passed away, the kidneys are paler than usual and the texture is quite flabby. Sections of the fresh tissues show in the cortex a considerable amount of pigment. In some cases the convoluted tubules are the elected seat of pigment deposit, and the epithelium of these tubes may be so filled with yellowish-red pigment that they are easily traceable in their windings by their decided color. Fatty changes are occasionally met with in the epithelium, and the straight tubules of the pyramids may be filled with fat globules. Degenerative or necrotic changes of the epithelium were not noticed in sections of hardened tissue from a few cases stained in various ways. In those cases in which the capillaries were filled with red corpuscles, the latter were usually all infected with Texas-fever parasites. The pelvis and its ramifications were usually found beset with blood extravasations.” For hæmoglobinuria of cattle, Starcovici states that the kidney capsule is hemorrhagic; a large hemorrhagic spot is present over each kidney, extending to the peritoneum. The kidneys are large, stiff, brittle, and dark red. The lining membrane of the pelvis is swollen and ecchymotic. The kidney changes consist in an overfilling of the vessels, and especially of the glomeruli, with blood, and peculiar desquamative and fibrinous yellow masses in the lumina of the uriniferous tubules, the epithelia of which appear compressed and show parenchymatous alteration.

For canine piroplasmiasis, Nuttall (1904, pp. 236–237) records that according to Hutcheon the kidneys are more or less congested, at times edematous, with dark-brown cortex; according to Robertson, they are pale and friable; in France they are usually greatly congested, and the capsule strips easily, revealing numerous petechiæ; on section, the cortex seems to be congested, and shows petechiæ; blood from kidney is very rich in parasites; in an acute case, yellowish-red fluid exuded on section.

In case 11 (1904) the gross appearance of the left suprarenal was apparently normal; the right suprarenal appeared congested, otherwise normal.

## BLADDER.

Wilson and Chowning (1904a, p. 42) report that upon autopsy the bladder was normal, and contained a small amount of urine which was darker than normal. Anderson (1903c, pp. 33, 38) reports the wall of the bladder apparently normal, the contents about 4 ounces of urine (case 120).

In case 3 the ventral wall of the bladder was congested; 1 ounce of urine of normal color was present. In case 89 the bladder and urine (about 3 ounces present) were normal. In case 91, 2 ounces of urine of normal color were present. In case 107 about 1 to 2 ounces [or  $\frac{1}{2}$  ounce?] of apparently normal urine was present.—Wilson and Chowning, 1903a, pp. 48, 52, 55.

Anderson (1903c, p. 33) reports for case 120, that the bladder was apparently normal and contained about 4 ounces of urine.

COMPARISONS.—Smith and Kilborne (1903) report for Texas fever that the bladder may show a few echymoses on its inner surface, and most cases contain 1 to 4 quarts of urine holding more or less hemoglobin in solution.

In hemoglobinuria of cattle the bladder is filled with dark red to black urine, which contains much hemoglobin, but usually no red-blood corpuscles.

In carceag, the bladder contains pale to red-brown urine with hemoglobin.

For canine piroplasmiasis, Nuttall (1904, pp. 236-237) says that the bladder may appear normal (Hutcheon, Robertson), and may contain urine which is generally dark brown like "pontac." In France prune-juice-like urine is found in an acute case.

## URINE.

*Quantity.*—*Idaho.*—In the Idaho cases the urine is reported as "scanty" by Bowers (1896, p. 64), Fairchild (1896), Springer (1896, p. 62), and Maxey (1899, p. 435).

*Montana.*—For Montana patients the urine is reported as reduced to one-half its normal amount (Wilson and Chowning, 1902a, p. 133; 1903a, p. 64; 1904a, p. 40; Anderson, 1903c, pp. 21, 23). Gates (1903, p. 49) gives it as 32 ounces for 24 hours following his first visit to 1 case; it then gradually diminished until 2 days before death, when there was complete anuria. Later (1905, pp. 111-113), Gates reports the urine as lessened in amount in case 11; much lessened at times in case 15; very scant at end of 1st week in case 16, but increased to normal amount by end of 2d week.

Wilson and Chowning (1903a, p. 58) give the urine in the bladder as normal in case 94.

In 1904 in case 3 urine was passed normally on May 10, and abundantly and involuntarily on May 15; in case 5 it was passed normally; in case 7 it was regular; case 11 passed 6 ounces in 24 hours on June 25 and 8 ounces in 24 hours, June 26; in cases 12 and 13 it was scanty.

The quantity of urine was not measured regularly.

*Color.*—For *Idaho* patients the urine is reported as of high color (Bowers, 1896, p. 64; Fairchild, 1896; Maxey, 1899, p. 435).

For *Montana* patients it is reported as "slightly above normal in color or as highly colored" (Wilson and Chowning, 1902a, pp. 132, 133; 1903a, p. 64; 1904a, pp. 37, 40); Anderson (1903c, p. 17) reports it highly colored in case No. 97; Gates (1903, pp. 48, 49) reports it as highly colored in one case and dark in another case. Later, Gates (1905, pp. 111-113) reports the urine as almost brown in case 11; highly colored in case 14; and dark in case 15.



In 1904, the urine was reddish yellow and turbid in cases 5 and 11, with a heavy yellowish precipitate in case 11: it was of high color in case 13.

*Specific gravity.*—For *Idaho* cases it is reported as of high specific gravity by Bowlers (1896, p. 64).

In 1904, the specific gravity was 1018 for case 11, 1022 for case 9, 1028 for case 5, and 1030 for case 13.

*Reaction.*—Maxey (1899, p. 435) gives it as acid in *Idaho*.

In 1904 the reaction was acid in cases 5, 9, and 11.

*Albumen.*—In *Idaho* cases no albumen was found by Fairchild (1896) and Maxey (1899, p. 435).

In *Montana* Wilson and Chowning (1903a, p. 64; 1904a, p. 40) found a small amount of albumen in each of 5 cases examined. Anderson (1903c, p. 23) states that a small amount of albumen was found in all cases examined, but his protocol of case 121 (pp. 34-37) denies albumen for this case; he gives albumen (pp. 31, 32) for case 120. Gates (1903, pp. 48, 49) gives slight amount of albumen for one case when first seen, and also for another case during the second week, while it was absent when first seen. Later (1905, pp. 111-113) Gates reports some albumen for his case 11; none for case 14; a trace in case 15; some albumen was found at times in case 16.

In 1904 albumen was found in case 5 (May 18), a trace was present in case 9, and a small amount in case 11. No albumen was found in cases 12 and 13. In none of these cases was a daily test made.

*Sugar.*—No sugar was found in 1904 in cases 9, 11, 12, and 13.

*Urea.*—Urea was 3.5 per cent in case 11 (1904).

*Bile.*—No bile (Gmelin) was present in case 11 (1904).

*Casts.*—Both granular and blood casts were found in each of 5 cases examined by Wilson and Chowning (1903a, p. 64), and later (1904a, p. 40) in 4 additional cases. Anderson (1903c, pp. 21, 23) states that granular, hyaline, and epithelial casts may be found; (p. 36) he found no casts in case 121; no casts (p. 31) were found in case 120 on May 8, but granular and epithelial casts were present on May 11. Gates (1903, p. 49) reports some hyaline and granular casts for one case when first seen (May 11), and an enormous number of granular, blood, and epithelial casts for the same case in the last sample [date?] taken. Later (1905, p. 112) he reports numerous blood and epithelial casts for case 15 (1904), and says that the urine of case 16 contained many blood and epithelial casts, but later, by the end of the second week, it was free from casts.

In 1904 granular casts were abundant in case 9. Case 11 contained abundant vaginal and small round epithelial cells, and numerous blood, epithelial, and granular casts, also much granular débris.

*Hematuria.*—Anderson (1903c, pp. 31, 32) found no red blood cells in case 120, and Gates (1903, p. 49) reports red and white blood cells in the last sample taken in one case. See also blood casts, under "Casts," above, p. 84.

In 1904 case 9 showed no blood. Case 11 showed free red and white blood cells (Ashburn).

*Hemoglobinuria.*—Hemoglobinuria is reported as absent or very slight by Wilson and Chowning (1903a, p. 64; 1904a, p. 40).

*Deposits.*—Maxey (1899, p. 435) says, in reference to *Idaho* cases, that the "urine



is loaded with amorphous urates," and Anderson (1903c, p. 31) reports heavy deposit of phosphates in case 120, in *Montana*.

*Post-mortem*.—Anderson (1903c, p. 38) states that usually a small quantity of highly colored urine is found in the bladder on post-mortem examination. (See under Bladder, p. 83.)

COMPARISON.—For Texas fever, Smith and Kilborne describe the urine as follows: "Next to the high temperature the condition of the urine demands our attention. The one sign regarded as peculiar and pathognomonic in this disease is the discharge of urine having the color of blood. This color is not due to a discharge of blood from the kidneys and subsequent breaking up of the red corpuscles, but to a filtration of the coloring matter of broken-down red corpuscles (hæmoglobin) already in solution in the circulation into the urine in the excretory structures of the kidneys. This fact was first pointed out in 1868 by R. Cresson Stiles. In using the term hæmoglobinuria this is all that is meant in this report. \* \* \* Hæmoglobinuria may be said to be present in most acute fatal cases of Texas fever. Out of 46 fatal cases in which urine was in the bladder after death, hæmoglobin was present in 33 cases. A careful examination of the notes will show that in 13 negative cases the animals were killed in the earliest stages of the fever, or else they died or were killed after the number of blood corpuscles had been greatly reduced and the acute stage of the disease was over. In the former cases the hæmoglobin had not yet been set free from the corpuscles; in the latter cases it had probably been eliminated one or more days before death. How frequently 'red water' is passed before death we can not state with any degree of certainty, since its discharge may wholly escape observation. We have a record of hæmoglobinuria in but four cases: In No. 43 on the third day before it was killed (probably 12 to 24 hours before death), and in No. 198, 24 hours before death. In some of these cases it so happened that the urine was passed while the animal was undergoing examination. It is interesting to note in connection with the statements made that in No. 44 no 'red water' was found in the bladder after death, although it had been passed 4 days previously. Whether hæmoglobinuria is always present in acute cases of Texas fever, it is impossible to state definitely. As it seems to depend upon the rapidity with which the red blood corpuscles are infected and destroyed, a slower destruction may allow other organs to take charge of the debris and thus forestall the discharge of hæmoglobin in the urine. In the notes will be found the record of hæmoglobinuria in but one acute case which recovered (No. 49), while in a number of cases in which the urine was collected, sometimes in the height of the fever, sometimes after it had departed, no hæmoglobinuria was detected. In this solitary case the high temperature first appeared August 18. On August 23, the temperature being still above 105°, the urine was free from hæmoglobin, but contained a small quantity (0.05 per cent) of albumen. On August 27 the temperature had become normal, but a second paroxysm followed soon after, and on September 4 and 5 the urine was of a port-wine color. Urine collected September 6 was again of normal color. The urine during the fever, when free from hæmoglobin, contains in many instances a small quantity of albumen. The specific gravity may at first be high (1,030 to 1,040), and it may be strongly alkaline and effervesce with acids as in health, but, as the disease progresses, and when the animal eats but little, its specific gravity will fall to 1,010 to 1,020; it fails to effervesce with acids and is faintly alkaline or even slightly acid. When the fever has subsided the urine has been observed to be in a few cases very watery, i. e., of very low specific gravity and feeble in color. Within one or two weeks, however, the normal condition is restored.

"The urine which contains the coloring matter of the blood varies, as might be expected, very much in depth of color, according to the concentration of the hæmoglobin. It may have a very light claret color, or it may be so deeply tinted as to appear opaque and blackish. In a test tube when viewed by transmitted light it may barely permit the light to pass unless diluted with water. Such urine is, as a rule, entirely

free from suspended matter and blood corpuscles. The latter may sometimes be found in small numbers when the urine is permitted to stand, and they may be derived from small hemorrhages in the pelvis of the kidney, quite regularly observed at autopsies. The coloring matter, as has been stated above, is derived from corpuscles broken up within the circulation, and not outside in the bladder. When such urine is treated with a little acetic acid a brownish flocculent precipitate, probably of the derivatives of hæmoglobin, appears. When boiled, a brownish flaky precipitate forms, which rises to the surface as a scum. As might be expected such urine always reacts in the presence of the usual tests for albumen. \* \* \* Suffice it to say that in very opaque urines the precipitate is quite abundant and corresponds when Esbach's test is applied, to from 1 to 3 per cent of albumen.

"The \* \* \* hæmoglobinuria is \* \* \* occasionally observed during life, and probably with the aid of a catheter may be seen much more frequently. \* \* \* Very little need be said of the other characters of 'red water.' When found in the bladder after or collected shortly before death its specific gravity is usually low (1,010 to 1,020) and it is feebly alkaline or acid. There is no effervescence with acids. After standing, a few granular casts and rarely urates are found in the very slight sediment. The greater the number of days before death that it is collected the more nearly it approaches normal urine as regards specific gravity and alkalinity."

Starcovici reports bloody urine as regular in the severer cases, but not observed in the lighter forms of bovine hemoglobinuria. In carceag bloody urine is less frequent.

For canine piroplasmiasis, Nuttall (1904, pp. 232-233) reports as follows:

South Africa: "All cases I have observed have been acute, and hæmoglobinuria was present, also albuminuria. The urine was claret or brownish-red in color, or resembling coffee grounds. Lounsbury and Robertson consider this brown coloring an unfavorable symptom, indicating a fatal termination. Hæmoglobinuria was noted by Hutcheon (1899). It may be absent in fatal cases, as in redwater (Robertson, p. 329). In one urine I examined I found the reaction acid, albumen, hæmoglobin, bile salts, and pigments, a considerable deposit consisting of spermatozoa (chiefly), granular casts, epithelium, leucocytes, granular detritus, crystals of salts, and a few erythrocytes. There were no spermatozoa or bile salts and pigment present on the day preceding death (dog 1). No hæmoglobinuria was observed in the chronic case recorded in Chart V."

France: "In acute cases urine albuminous at onset before parasites can be found in the blood. Albuminuria persists until death, increasing with number of parasites present. Hæmoglobinuria: Urine pink, dark red, blackish, like prune juice or coffee grounds, according to its degree. No erythrocytes in urine. Oxyhæmoglobin may amount to 2.5 per cent. Hæmoglobinuria appears soon after parasites are seen in the blood, and in very acute cases persists until death, and is found in bladder at autopsy. Hæmoglobinuria inconstant, noted in 3 out of 6 cases by Nocard and Almy; this may be due to its being at times very transitory. Nocard and Motas observed more or less lasting and severe hæmoglobinuria in 43 out of 63 dogs. Bile pigment present in cases showing icterus and hæmoglobinuria. Reaction acid only found neutral twice, alkaline once. Polyuria rare.

"In chronic cases urine usually slightly albuminous at start, condition lasting 15-20 days. Hæmoglobinuria very rare; lasts 1 to 2 days. Urine may be icteric. Reaction acid only once found neutral; this attributable to other causes (sugar found)."

It will thus be seen that while Wilson and Chowning report hæmoglobinuria as absent or very slight in "spotted fever," this is a prominent symptom in piroplasmic diseases. If, therefore, "spotted fever" is a piroplasmiasis, it differs in this very characteristic symptom quite markedly from other maladies caused by parasites of the same genus.

See *Genitalia*, page 55.

Several women have been taken sick while pregnant. Case 121 was two months pregnant (Anderson, 1903c, p. 34), but apparently did not abort.

Wilson and Chowning (1904a, p. 42) report the uterus as apparently normal in the 3 females examined.

In case 11 (1904) patient aborted; the uterus, upon autopsy, measured 11 by 13 cm., was soft, but normal in appearance for a recently delivered uterus; on section it was normal; the vagina showed slight bloody discharge; the ovaries were normal; right ovary contained corpus luteum.

In case 3 menstruation occurred for one hour on May 14, and then stopped; it began again during the night of May 14-15, and flowed freely until death. Her former menstruation was on April 11, so that the disease appears to have delayed her menses. Case 5 menstruated just prior to attack.

#### RELAPSES.

Case 53 (Gwinn's patient, 1899) relapsed after abortive treatment (Wilson and Chowning, 1903a, p. 35; Anderson, 1903c, p. 15). According to Gwinn (1902) relapse is favored by getting up from bed too soon, or by muscular exertion, or exposure to cold.

We saw no relapses in 1904.

COMPARISON.—In carceag there is usually 1 attack; in some cases there is 1 or 2 days of remission, then a second attack.

#### COMPLICATIONS.

*Idaho*.—Some cases develop rheumatic trouble, particularly of the larger joints.

*Montana*.—Hypostatic pneumonia, rheumatism, gangrene, and hemorrhagic diathesis seem the most usually to complicate the disease (McCullough, 1902, p. 226); pneumonia predominates in frequency as a complication, and such involvement of the lungs along with the predominating illness generally terminates the case.

Hypostatic pneumonia is a frequent complication for a day or so before death; one case had to all appearances genuine lobar pneumonia; one case gave well-marked symptoms of acute inflammatory rheumatism as complication; one case was complicated with abscess and gangrene (Gwinn, 1902).

The symptoms noted are sometimes complicated by gangrene, hypostatic pneumonia, articular rheumatism, etc.; hypostatic pneumonia sometimes develops; lobar pneumonia occasionally occurs as a complication, and usually hastens the end (Wilson and Chowning, 1904a, p. 40).

According to Anderson (1903c, p. 23) lobar pneumonia is a frequent complication in fatal cases; cases 44, 74, and 75 were complicated with pneumonia (1903c, p. 15).

#### CONVALESCENCE.

*Idaho*.—Convalescence is established during the third week, and is usually prolonged (Bowers, 1896). It is remarkably slow; and may be prolonged for months (Dubois, 1896, p. 64). It usually begins by or follows a stage of profuse sweating (Fairchild, 1896), and during convalescence the cough remains (Figgins, 1896, p. 64). Sweet (1896, p. 61), on the other hand, states that convalescence is usually rapid.

*Montana*.—Convalescence in case 78 began at the end of 23 days, and about the



twelfth day in case 103. It was very slow in cases 113 and 114, 10 or 12 weeks passing before the patients were able to work; health afterwards was not so good (Anderson, 1903c, pp. 14, 15, 16, 17). See also Duration, page 42.

Gates reports that his case No. 15 suffered from severe intercostal neuralgia during convalescence.

COMPARISONS.—In carceag convalescence lasts about 14 days.

#### PROGNOSIS.

*Idaho.*—Delirium or involvement of the nervous system is a bad prognostic sign; the amount of fever is deceptive, as fatal cases may have a temperature not exceeding 103° (Bowers, 1896, p. 64). Prognosis is, as a rule, quite favorable, if the patient is transferred to the lower valleys, where he can have home comforts and proper care; the disease appears to be more malignant in some localities than it is in others; the recovery is, in the majority of cases, complete (Maxey, 1899, p. 438).

*Montana.*—If the patient be promptly and thoroughly treated as here set forth (see below, p. 92) within 12 to 24 hours after the onset, nearly all attacks can be abated; but when the case is seen later, and the disease be not broken up, about 60 per cent or more prove fatal (Gwinn, 1902). In milder cases, where symptoms are not so marked, in which the jaundice, delirium, high temperature, eruption, and systemic infection are slight or entirely absent, the prognosis is usually favorable; it is very grave in typical severe cases, but there is no doubt that many mild and moderately severe cases recover; where the systemic infection is pronounced, jaundice very plainly discernible over entire body, delirium of low muttering type, hemorrhagic diathesis portrayed in the dusky appearance of the eruption, these cases invariably die; typical cases run a well-defined course, and patients surviving the fourteenth to sixteenth day are likely to recover (McCullough, 1902, pp. 25, 27).

In Montana, cases of the mild type of the disease, which show no spots, are as yet too indefinitely differentiated to permit of their inclusion with those of the severe type which invariably develop the eruption; that such cases exist there can be no doubt; they are never fatal; on the other hand, the cases which are marked by the eruption have a mortality of 70 to 80 per cent (Wilson and Chowning, 1902a, p. 133; 1903a, p. 65; 1904a, p. 40). It is unsafe to prognosticate a favorable termination in a case of mild initial symptoms, since many such cases rapidly become fatal (Wilson and Chowning, 1903a, p. 66). Prognosis of cases in Idaho, Nevada, and Wyoming is much more favorable (Wilson and Chowning, 1904a, p. 41).

The abundance of the eruption apparently bears no relation to the severity of the disease (Anderson, 1903c, p. 39).

Gates (1905, p. 115) states that in his experience the cases in children have been mild.

#### LETHALITY.

See also page 37.

*Idaho.*—The lethality is about 2.5 per cent; in fleshy subjects the disease is a serious affection, but particularly in the aged it is fatal; from the fifth to the eighth decade the lethality progressively increases from 5 to 50 per cent (Bowers, 1896, p. 64). Collister (1896, p. 63) reports that the death rate is not very high; in children it will not exceed 1 per cent, and in old age it varies from 4 to 5 per cent. According to Dubois (1896, p. 64), the lethality persists during the entire attack from 14 to 28 days; it is not high, but weak subjects, and even strong ones, succumb from intercurrent affections of the bowels, kidneys, or heart; it may be called a nonfatal disease. In Fairchild's experience (1896) the death rate is low, perhaps 2 or 3 per cent. Figgins (1896, p. 64) has seen but 1 fatal case in about 60 cases he treated, extending over a period of 14 years; death in this case, he believes, was superinduced by years of dissipation and by age. According to Springer (1896, p. 62) the death



rate is probably about 1 or 2 per cent, but higher in old people; death usually occurs from exhaustion. Sweet (1896) says that the death rate is slight, and Zipf (1896, p. 65) states that the disease is very seldom fatal; he has heard of only 1 fatal case this year (1896), and this patient had always been of weak constitution.

*Montana.*—Spotted fever is very fatal, but perhaps not more so than Asiatic cholera or yellow fever; it is more fatal in adult males than in women and children. Hanbidge reports 12 fatal cases in 16; Gwinn, 30 fatal in 40 severe cases; St. Patrick Hospital, 12 fatal in 15; McCullough, about 75 per cent fatal (McCullough, 1902, pp. 225, 227). Anderson (1903c, p. 38) gives the case mortality as about 70 per cent. The mortality varies within narrow limits from year to year; some years as many as 90 per cent of those attacked dying. Wilson and Chowning (1903a, p. 65; 1904a, p. 41) give tables showing the case mortality for various ages of males and females (see above, under "Sex and age," p. 37). Cases which are marked by the eruption have a mortality of 70 to 80 per cent, but cases without the eruption are never fatal (1902a, p. 133; 1903a, p. 65; 1904a, p. 42).

COMPARISON.—In Texas fever the lethality varies greatly. The time of the outbreak will largely decide whether practically all of the animals attacked die or all survive; a midsummer outbreak, when acute in its nature, is the most fatal. From this there may be all gradations toward the mild, nonfatal form of late summer. (Smith and Kilborne, 1893, p. 23). Starcovič gives the lethality as about 50 per cent for hemoglobinuria and 50 to 60 per cent for carceag.

In Texas fever death usually occurs from the fourth to the fourteenth day; in hemoglobinuria, in various stages of the disease; in carceag, usually from the second to the fifth day.

#### DEATH.

*Idaho.*—Death in adults and the aged results from toxemia and exhaustion (Bowers, 1896, p. 63). Death usually results from exhaustion (Springer, 1896, p. 62). It is usually due to lowered vitality from other causes, such as bad air and surroundings (Sweet, 1896).

*Montana.*—Wilson and Chowning (1904a, p. 41) have tabulated 88 cases with reference to date of death and have shown that in 69 of these death occurred from the sixth to eleventh days, inclusive. Adding to these statistics the cases recorded by Gates and those I have collected we find that death occurred on the—

	Cases.		Cases.
Third day in .....	1	Twelfth day in .....	6
Fourth day in .....	1	Thirteenth day in .....	4
Fifth day in .....	3	Fourteenth day in .....	2
Sixth day in .....	13	Fifteenth day in .....	2
Seventh day in .....	13	Eighteenth day in .....	1
Eighth day in .....	14	Twenty-second day in .....	1
Ninth day in .....	11	Twenty-seventh day in .....	1
Tenth day in .....	13	Twenty-ninth day in .....	1
Eleventh day in .....	9		

#### DIAGNOSIS.

##### SPECIFIC DIAGNOSIS.

*Idaho.*—After once seeing and recognizing spotted fever the diagnosis is easy; there is no occasion for making a mistake; even the laity recognize it on sight; its peculiar habitat and endemic character, the severe aching pains in the muscles, joints, bones, and head, the absence of gastro-intestinal symptoms, the temperature range, the

invariable appearance on the third to the seventh day of a profuse eruption of rose-colored, unelevated spots, first noticeable on the wrists and ankles, and rapidly spreading over the entire body, the frequency of constipation, and the marked debility noticeable during convalescence all go to make up a clinical picture characteristic only of spotted fever; in 3 or 4 cases in which I have used Ehrlich's diazo test the result has been negative (Maxey, 1899, pp. 436, 437). Epistaxis (see, however, p. 52), diarrhea, iliac tenderness, and gurgling are said to be seldom, if ever, present (Medical Sentinel, p. 457).

*Montana.*—Generally bad feeling, coated tongue, constipation, accelerated pulse and temperature, the expression denoting profound intoxication of the entire system with some grave illness, the unusual, intense soreness all over the body, affecting both bones and muscles, perhaps more marked along the spine and back of the neck and head, the icterus appearing from the fifth to tenth day of illness, and the characteristic eruption following, leave little room for doubt regarding the type of illness with which we have to contend (McCullough, 1902, p. 226).

According to Anderson (1903a, p. 508, 1903c, p. 39), cases occurring in infected localities and presenting a history of tick bites, chill, pain in head and back, muscular soreness, constipation, macular eruption, first on the wrists and ankles, appearing on the third day of illness, becoming petechial in character, do not present difficulty in diagnosing spotted (tick) fever; blood examination should be made in all suspicious cases.

While the different cases of spotted fever vary to no inconsiderable degree, this variation in symptomatology is perhaps not greater than it is in many other diseases. As for the blood examination to find the parasite, as a test in diagnosis, I must take the position that this is not at present upon a firm foundation. Ashburn and I are as expert with the microscope as the average physician, yet we were not able to find the parasite in the cases we examined, although we spent a total of 400 hours of actual microscopic work, equivalent to 80 days' work of 5 hours each.

#### DIFFERENTIAL DIAGNOSIS.

*Idaho.*—This disease differs principally in the occurrence of the symptoms from our occasional mountain fever, which seems to be similar to the mountain fever of the eastern Rocky Mountain region, a typhomalaria, or at least a modified typhoid (Sweet, 1896). "As I have known physicians to call it 'dengue fever,' cerebrospinal meningitis, typhoid, rheumatic purpura, typhus, and measles, I may be pardoned for taking up the differential diagnosis and calling your attention to the salient points of difference in support of the theory that this spotted fever is an independent, specific disease, and related in no way to any disease described in our text-books on practice."—Maxey, 1899, p. 436.

#### TYPHUS.

*Idaho.*—Maxey (1899, p. 438) states that he has known one or two physicians who invariably diagnosed spotted fever as "typhus fever," but he calls attention to the fact that typhus is an epidemic, contagious, malignant disease, more prevalent in the winter season and in thickly populated or crowded districts, and attacks men, women, and children alike; the onset is abrupt, with chill, followed by a violent fever and pain in the head; the eruption, red and measly, appears on the fifth to seventh day; there is also a peculiar mottling of the skin all over the body except the face.

*Montana.*—"Spotted fever more nearly resembles typhus fever than any other continued fever with which I am familiar, with the exception that it is not conta-

gious" (see above, p. 44).—McCullough, 1902, p. 225. Gwinn (1902) says: "I have been unable to find any marked difference by which to distinguish it [spotted fever] from this disease [typhus], save that typhus is by most authors given as a contagious disease, while the affection under discussion certainly is not contagious, and does not occur in crowded, filthy places, like jails, etc., as does typhus. Had this difference not existed I should never have claimed that this disease was one not described by medical literature. That one is contagious while the other is not is such a radical difference that one can not be justified in calling them the same. Either we have a disease to contend with heretofore undescribed by authors or most of our authors are mistaken as to the contagiousness of typhus." Anderson (1903c, p. 40) says: "Spotted (tick) fever, I think more closely resembles typhus fever than other disease, and cases of typhus fever occurring in a locality in which spotted fever prevails would, without a blood examination and close bedside observation, cause much trouble in diagnosis. In typhus we have a longer period of incubation, absence of a history of tick bites, the eruption which first appears on the abdomen and chest, its intensely contagious character, especially prevalent in the winter months, not limited to a short time in the spring, and marked nervous symptoms. As before mentioned, two cases of spotted fever have never been known to occur in the same family the same season (see, however, above, p. 43), thus conclusively showing the noncontagious character of the disease."

#### TYPHOID.

*Idaho*.—Many patients after a few days pass into a typhoid condition (Springer, 1896, p. 62). Epistaxis, diarrhea, and other abdominal symptoms, the scattering, petechial eruptions not appearing until the end of the first week, the absence of severe pains in the muscles of the limbs and back, the nerve symptoms, the characteristic tongue, and the greater prevalence in the autumn, render the differentiation quite plain; in the 3 or 4 cases of spotted fever in which Ehrlich's diazo test has been used the result has been negative (Maxey, 1899, p. 437).

*Montana*.—At the onset, the whole facies in spotted fever is in certain respects typhoid (Wilson and Chowning, 1902a, p. 132; 1903a, p. 62; 1904a, p. 37). Anderson (1903c, p. 39) says that typhoid resembles spotted fever, but the rose spots appearing first on the abdomen—papular in character—diarrhea, Widal reaction, and presence of typhoid bacilli in cultures from the blood of typhoid fever, and the presence of parasites in the red cells of spotted fever (see, however, above, p. 90), suffice to separate distinctly the two diseases.

#### MENINGITIS.

*Idaho*.—Before death, children have symptoms of meningitis (Bowers, 1896, p. 63). Maxey (1899, p. 437), in speaking of meningitis, refers to its occurrence in winter, its malignancy, its predilection for children, sudden onset with chill or convulsion, the severe headache or vomiting, painful rigid or contracted condition of the muscles of the back of the neck, with opisthotonos, the irregular fever, the scattering petechial or purpurial eruption not present in all cases, the hyperesthesia, disorders of special senses, stupor or coma.

*Montana*.—Gwinn (1902) mentions in one case rigidity of the muscles of the neck and back, very much resembling that of cerebrospinal meningitis; when spotted fever is seen after the eruption begins to darken it may be distinguished from cerebrospinal meningitis by the absence of the typical vomiting, the rigidly contracted muscles of the neck and back, the herpes, and the irregular, low-averaging temperature of the latter disease. McCullough (1902, p. 225) considers spotted fever as distinct from meningitis. Anderson (1903c, p. 39) says in reference to meningitis that "the stiffness of the muscles of the neck, photophobia, sensitiveness to sudden noises, headache, and rigidity of the muscles of the back and neck, with the not altogether constant irregularly situated rash, should not cause much trouble."



It seemed to me that cases occur which are not so easily differentiated symptomatically from some cases diagnosed as cerebrospinal meningitis, as the above remarks would lead one to believe. However, "spotted fever" does not show post-mortem lesions which would justify us in classifying it as meningitis. (See also page 79.)

## DENGUE.

*Idaho.*—Dengue or breakbone fever is an epidemic, contagious disease, found only in subtropical climates. Its onset is abrupt with chill and intense pains in head and back, followed by high fever for from 1 to 5 days, when there is an intermission of all symptoms for a day or two, followed by a second paroxysm of fever and pain. There is a scarlatinal rash during the first paroxysm, and a characteristic erythematous rash or rubeolus eruption accompanies the second paroxysm. Nausea and vomiting are common, and the average duration is only 8 days (Maxey, 1899.)

*Montana.*—Dengue is a disease of tropical or subtropical countries, whereas spotted fever occurs at an elevation of from 3,000 to 4,000 feet above sea level. The swollen joints, pleomorphic eruption over the joints, never petechial, apyretic period, and short course of the disease would differentiate it from spotted fever (Anderson, 1903c, p. 39).

## PURPURA HEMORRHAGICA.

Purpura hæmorrhagica occasionally accompanies severe cases, the hemorrhagic spots becoming as large as the thumb nail (McCullough, 1902, p. 226). Purpura in this region [Bitter Root Valley] is manifested by the eruption being generally confined to the lower extremities, a less systemic disturbance than in spotted fever (Gwinn, 1902).

## PELIOSIS RHEUMATICA.

In peliosis rheumatica, the sore throat, multiple arthritis with purpura and urticaria, and comparative rarity of the disease, offer a sufficiently distinct clinical picture (Anderson, 1903c, p. 39).

## "BILIOUS FEVER."

"If seen at first, and it be a mild attack, it [spotted fever] very much resembles bilious fever or biliousness with constipation. However, if the patient has been chilly and the skin appears congested, the eyes congested as well as jaundiced, and it be at a locality and time when this disease may be suspected, it should not be overlooked in the diagnosis. If it be a severe attack, the danger of mistaking the two diseases is very much lessened by the pronounced chill, high fever, and inordinate aching, they being more severe than in biliousness" (Gwinn, 1902).

## MEASLES.

*Idaho.*—If a case of spotted fever is not seen until the spots are well out, it might be mistaken for a case of measles; but when we take into consideration the epidemic and contagious nature of measles, the characteristic catarrhal symptoms referable to the respiratory tract, the elevated, crescentic, crimson eruption, and the presence of Koplik's spots, we should not hesitate long (Maxey, 1899, p. 438).

*Montana.*—When the eruption is new it may be mistaken for that of measles, but close examination shows the eruption to be purely macules, and not in the least elevated (Gwinn, 1902).

## TREATMENT.

## GENERAL PRINCIPLES.

*Idaho.*—"No abortive or reliable curative treatment has as yet been discovered. The disease is self-limited and a large portion of cases recover without any internal medication. Treatment of individual cases is governed by the rational and symp-



tomatic conditions present. On the theory that the infection enters through the alimentary canal, I employ intestinal antiseptics and evacuants and a supportive treatment."—Bowers, 1896, p. 64. "No medication will relieve the pain and fever; but quinine, dissolved in aromatic sulphuric acid, in comparatively large doses, gives the best results to those who can withstand the treatment."—Dubois, 1896, p. 64. "It is a self-limited disease, and drugs have little or no effect upon the attack. I treat on expectant plan principally. When pain is severe I control it with morphia, and to lessen the hyperæmia of the cord, etc., I usually give a mixture of bromide and ergot. When temperature goes above 103° F., I bathe with tepid water, and, if indicated, give small doses of acetanilid or phenacetin. Quinine has given no results in my hands. I keep patients in a recumbent position constantly, overcome constipation with salines, and confine them to a milk diet."—Fairchild, 1896. "I never employ any other than such as is used in ordinary malarial fevers, and that of symptomatic nature."—Figgins, 1896, p. 64. "Expectant. Morphine for pain; salines for constipation; sponge baths and antipyretics for high temperature. Diet, milk."—Springer, 1896, p. 62. "Milk diet; a cholagogue followed by frequent alcohol hot baths, with usually very little positive medication. As routine, I usually relieve the dengue ache with salol, quinia salts, and some coal-tar products in very small doses until free diaphoresis is obtained. I give little but a placebo in mild cases."—Sweet, 1896. "Treatment is entirely symptomatic. The hygienic and sanitary surroundings should be the best possible to obtain. Frequent baths and changes of bedding add materially to the patient's comfort. For the fever I usually use cold sponging, with occasional doses of acetanilid or phenacetin and codeine, or Dover's powders may be required to relieve the pain and restlessness. During convalescence stimulants, iron and bitter tonics are in order."—Maxey, 1899, p. 438.

*Montana.*—"I have tried many remedies, but found most of them to do but little or no good, and often harm if they should be pushed in amount or number. The treatment which has served me best is what might be termed eliminative and supportive treatment. The old rule of keeping the head cool and feet warm should be closely observed. The patient should be frequently turned in bed after the disease is well established, in order to prevent hypostatic pneumonia, and to cool the underside of the body, which may be superheated while the upper side is cool."—Gwinn, 1902. "The best results are obtained by systematic and eliminative treatment" (McCullough, 1902, p. 227). "Until the past season [1903] the treatment of this disease has been purely symptomatic, but after the discovery of the parasite, Doctor Wilson and the writer suggested the use of quinine in large doses, preferably hypodermatically" (see below, p. 94).—Anderson, 1903c, p. 40. "Many drugs have been used in the treatment of 'spotted fever,' but while some of them are important as stimulants, sedatives, etc., none of them—except perhaps quinine—seem to have any specific action on the disease through destruction of the parasites."—Wilson and Chowning, 1904a, p. 57.

#### SURROUNDINGS.

"The room should be kept dark and as free from noise as possible."—Anderson, 1903c, p. 41. "Darkening of the room and hot sponge baths add much to the comfort of the patient."—Wilson and Chowning, 1904a, p. 57.

#### DIET.

*Idaho.*—"The diet and bowels should be properly regulated, particularly after the eruption is well out, for I have found in the majority of my cases that at this time the appetite is apt to return to the patient, and the physician's judgment will be taxed to decide just what and how much food may be allowed."—Maxey, 1899, p. 438.

*Montana.*—"Milk, buttermilk, broths, soft eggs, and soft toast may all be allowed. The whisky may be administered in an eggnog."—Anderson, 1903c, p. 41.

## TICK BITE.

"As soon as a person is bitten by a tick, the insect should be removed and the place cauterized with 95 per cent carbolic acid. There is sometimes difficulty in removing the tick, but by applying ammonia, kerosene, or carbolized vaseline it can usually be detached without trouble."—Anderson, 1903a, p. 41.

"As soon as a person is bitten by a tick, the arachnid should be removed and the wound cauterized with a 95 per cent carbolic acid."—Wilson and Chowning, 1904a, page 56.

In 3 cases during 1904 in which this precaution was adopted it did not seem to inhibit the development of the disease, for all 3 patients died. Further, while the precaution may be good, so far as the tick bite is concerned, I do not see what good effect may be expected from it in aborting a piroplasmosis.

## PURGATION.

"To act on the bowels, if the patient be an adult and robust, I begin by giving 20 grains of the mild chloride of mercury well rubbed together with the same amount of sodium bi. carb., to be followed in 12 hours by an ounce dose of magnesium sul. This will keep the bowels active for 1 to 3 days, after which I give the same remedies in sufficient quantity to make the bowels act 2 or 3 times every 24 hours."—Gwin, 1902.

"For cases encountered within the first 3 or 4 days I begin with:  $\mathcal{R}$ . Hydrarg. chlor. mite et sodii bicarb.,  $\text{ãã}$ . gr. i. Tablets no. xii. Sig.: One tablet every half hour until all are taken.

"This rarely fails to produce free purgation and unloads the intestinal canal, thereby relieving any tendency to hepatic engorgement. Should catharis be insufficient, a clyster containing a teaspoonful of turpentine should be given. Then with a view of eliminating the noxious accumulations in the system, and in some degree modifying the jaundice, give:  $\mathcal{R}$ : Sodium phosphatis  $\mathfrak{z}$ ii. Sig.: Teaspoonful given in hot water every 3 hours.

"By administering this remedy at above-named intervals the bowels are kept free, diaphoresis increased, and muscular soreness diminished."—McCullough, 1902, pp. 227-228.

In case 118, bowels were kept open with calomel (Anderson, 1903c, p. 28).

## QUININE.

"In 5 cases in which it [quinine] was used systematically and in large doses the results were most happy, all recovering. Five cases which did not have the treatment died. Of course, 10 cases is too small a number on which to base very positive conclusions, but I hope that the use of quinine will be followed in the future treatment of the disease. Quinine bimuriate, 1 gram, should be given hypodermically every 6 hours. If there is great objection to the use of the needle, the sulphate, 1 gram every 4 hours, may be given by mouth; but the irritable condition of the stomach at times may prevent. The use of quinine should be begun as soon as the diagnosis is made, and persisted with in decreasing doses as convalescence begins. Some of the valley physicians seemed to fear that quinine depressed the heart and caused nervous symptoms; but I am of the opinion that the great good the drug does more than counterbalances these effects. I strongly advise the early and continuous use of large doses of quinine." Anderson, 1903c, p. 40. "The good results that have followed the administration of large doses of quinine—the 5 cases in which it was used having recovered—give much hope that this disease, which is so much dreaded, may in future be robbed of many of its terrors."—Anderson, 1903c, p. 7.

Quinine has been used by the physicians of the Bitter Root Valley in small doses by mouth for a number of years in the treatment of this disease. During the spring of 1902 the writers urged, on purely theoretical grounds, the use of large doses of the drug intravenously, hypodermically, or per rectum. Cases 94 and 95 were given quinine per mouth and rectum to the point of cinchonism, with some apparent beneficial results. Both cases died, though No. 95 was convalescent from spotted fever and died of a complicating pneumonia. During 1903 cases Nos. 115, 118, 119, 122, 124, 125, and 126 were treated with doses ranging from 5 grains by mouth (case No. 119) to 60 grains subcutaneously (case No. 118). All of these cases except No. 125 recovered, though case No. 119 died later of a complication (acute gastritis). Case 125 was an old debilitated man, and had the most abundant infection of all the cases examined by the writers. The remaining 5 cases occurring in 1903 and untreated with quinine were all fatal. These cases are too few on which to base conclusions, but are sufficiently suggestive to warrant a further trial of the treatment. In this connection it is worthy of note that Theiler (1903) has recently made the observation that in South African equine malaria, a disease caused by *Piroplasma equi*, the pyroplasmata rapidly disappear from the blood of infected horses on the administration of quinine and ammonium chloride."—Wilson and Chowning, 1904a, p. 57.

In connection with the cases which occurred in 1903, it may be noted that Gates's case (No. 10, 1903) was not reported as having been treated with quinine, but recovered. As this case was known to Anderson and to Wilson and Chowning, it must be concluded that they did not include it in the statements that the 5 cases which did not have quinine treatment died.

So far as I was able to learn, the quinine treatment in large or comparatively large doses is not new in the Bitter Root Valley. Doctor Mills, for instance, gave quinine in large doses per mouth some years ago, but his results were so unsatisfactory that he discarded its further use. Doctor Howard has been giving quinine for 6 years in large doses twice a day, and claimed to have had very good success with it up to 1904. He states that under quinine treatment 6 out of 7 cases recovered. Doctor McGrath has been using quinine for about 5 years; of 6 quinine cases 5 recovered. One physician has lost 2 or 3 cases under quinine treatment—3 grains every 2 or 3 hours. Doctor Brook informed me that one of his quinine cases died after 12 days of treatment; he also lost another quinine case. Doctor Gwinn used quinine from 1887 to 1890; some patients recovered, others died. He then rejected it. He tried it again about 1897, giving about 1 dram per day, but as all of these cases died he again rejected it. He used it in 2 cases in 1903, and one case recovered; the other died under the same treatment.

Quite a number of local physicians with whom I spoke maintained that except in imported malaria cases quinine could not be given in that locality so freely as in lower eastern and southern localities, without more serious effect, but this view was not shared by two other physicians.

Early in 1904 Doctor Mills stoutly combated the quinine treatment



on the ground that his experience with it had been so unsatisfactory. Ashburn also had grave doubts regarding its value and in case 3 he opposed it rather strongly.

In the 2 Bitter Root Valley cases of 1904 which recovered, no quinine was used, and in the 5 cases in which it was used the patients not only showed no improvement, but died; in cases 12 and 13 also it was not used and the patients recovered.

COMPARISONS.—In connection with the statement by Wilson and Chowning quoted above, that Theiler observed that *Piroplasma* in the blood of horses in South Africa rapidly disappear on the administration of quinine and ammonium sulphide, it might be added that Nuttall (1904, pp. 248-249), in discussing canine piroplasmiasis, says:

“Apart from the specific treatment recorded above, there is very little to note regarding treatment. In South Africa, Hutcheon (1893, p. 477, and 1899, p. 400) recommended the use of repeated doses of ammonium chloride and belladonna, a form of treatment tried by Borthwick at Port Elizabeth with ‘excellent results.’ Subsequently Hutcheon obtained encouraging results from the use of quinine, benzoate of soda, and carbolic acid. Robertson (1901, p. 332) states that he has tried quinine, calomel, ammonium chloride, extract of belladonna, carbolic acid, and finally benzoate of soda without satisfactory results. Carbolic acid appeared, in fact, to hasten death. He obtained the best results from a ‘calomel pill to start with, then a calomel and quinine pill four times a day.’ Without stating the dose, he says that very large amounts of calomel are needed. Hutcheon does not appear to approve of the calomel treatment. In other words, the evidence as to treatment in South Africa appears to be somewhat contradictory.

“In Europe, Piana and Galli-Valerio (1895) attributed the recovery of the one dog they saw suffering from Piroplasmiasis to the use of quinine. Almy (10, x, 1901, p. 379) treated his dogs with quinine bromhydrate, but observed no effect therefrom, the remedy being as ineffective as quinine has been shown to be in the treatment of Tristeza (*Piroplasmiasis bovis*).

“Evidently there is no known remedy for canine Piroplasmiasis, and it is open to question whether or no the dogs which have been successfully treated would not have recovered anyhow.”

#### CALCIUM SULPHIDE AND CREOSOTE.

“Some physicians speak well of calcium sulphide, and others of creosote.”—Anderson, 1903c, p. 40.

#### PAIN.

“For the severe pain in the head and back during the first week, Dover’s powders or morphine may be used.”—Anderson, 1903c, p. 40.

Morphine is used in this disease by a number of the local physicians, and Mills called my attention to the large doses which the patients could take. Case 11 (1904) in one day received 9 grains within 8 hours, and at another time 4.5 grains in 2 hours without noticeable effect.

#### SKIN.

“To produce an active skin, lower fever, and reduce pain, phenacetin acts well, and may be given as seems to be needed in 10 to 15 grain doses for a few days succeeding the attack, without lowering the patient’s vitality to a noticeable degree.”—Gwinn, 1902.



## BATHS.

"After from 2 to 4 days, when the chilliness has ceased and when the patient will tolerate cool baths, I substitute them for the phenacetin. It often occurs in the later stages of this malady that the surface of the body will be cold and the axillary temperature even below normal, resultant from the obstructed or weakened circulation, while the thermometer will show a high fever if registered in the rectum. In this event a blanket may be added to the patient's covering to warm the periphery and extremities of the body."—Gwinn, 1902.

Anderson (1903c, pp. 37, 40) reports that warm sponge baths or packs relieved the congestion of the skin, reduced the fever, and allayed restlessness; the spots became brighter after the bath.

## ENEMATA.

"An enema of cool normal salt solution lowers central temperature, and supplies the kidneys with fluid with which to eliminate poison from the system."—Gwinn, 1902.

## FEVER.

"For the fever warm sponges baths or packs are useful and refreshing to the patient. After a bath the spots lose their dark color and become much brighter."—Anderson, 1903c, pp. 40-41.

## DIURESIS.

"To produce an active diuresis I know of nothing better than to encourage the patient in drinking an abundance of fluid; potass. acetate and liq. amm. acetat well during the first stages, while digitalis is well given during the latter stages when also needed to support the heart. As a drink during the first stages I recommend water, lemonade, and buttermilk. I have seen excellent results from beer as a heart stimulant and diuretic after the patient becomes weak. All drinks should be cold and taken frequently in small amounts."—Gwinn, 1902. "The patient should be encouraged to drink large quantities of water to flush out the kidneys."—Anderson, 1903c, p. 40.

## HEART.

"For a fagged heart and respiratory effort I know of nothing better than strychnia, digitalis, and alcoholics."—Gwinn, 1902. "Heart action should be watched, and any tendency to weakness of that organ should be stimulated by one-thirtieth grain strychnia given hypodermatically as directed."—McCullough, 1902, p. 228. "The heart should be supported by strychnine, whisky, or other appropriate cardiac stimulants."—Anderson, 1903c, p. 40.

## DELIRIUM.

"For the active delirium and sleeplessness I have found no more effectual remedy than: R. Chloral hydratis et Kali bromidi āā. ʒiii; tinct. hyocyam., ʒii; flu. ext. glycyrrhiza. ʒss; aq. menth. pip. q. s., ʒiii. M. Sig. 2 teaspoonfuls in 2 tablespoonfuls of water when very restless, and repeat in 6 hours if needed.

"The high fever and moderate delirium call for the ice bag applied to the head, cold sponge bath if not too much body tenderness, and occasional 10-grain doses of antipyrine."—McCullough, 1902, p. 228.

## SALINE SOLUTION.

"Rectal and subcutaneous injections of normal salt solutions were given. The combined use of the above and hot packs, together with hot elder water and liquor ammonii acetatis internally, produced only slight diaphoresis, and that mostly about the head."—Gates, 1903, p. 49.

Normal salt solutions, in rectal, vesical, and subcutaneous injections, were repeatedly used in 1904 with good temporary effect.

## OXYGEN.

Oxygen was repeatedly resorted to in emergencies in 1904 with temporary good effect.

## BLEEDING.

Case 11 (1904) was bled twice with very marked temporary relief. On June 27, p. m., about 12 ounces of blood were taken, after which the patient had a good night's rest; the next morning the spots were much lighter in color. On June 28, p. m., about 1 ounce of blood was taken, followed by noticeable temporary improvement; the next morning the spots were lighter, but the patient died later in the day.

## SUPPORTIVE TREATMENT.

"As supportive treatment as well as germicidal, and having a particular action on the blood, I have found useful: *R.* hydrarg. bichlor., gr. i; liq. pot. arsenitis,  $\bar{3}$  ii; tinct. ferri chlor.,  $\bar{3}$  ss.; acid phos. dil.,  $\bar{3}$  i; syr. limonis q. s.,  $\bar{3}$  vi. *M. sig.* Teaspoonful in wineglass of water four times a day.

"In addition to the above medication, the special symptoms require careful treatment best adapted to such complications individually."—McCullough, 1902, p. 228.

## PREVENTION.

"In the way of prophylaxis, I have advised an occasional dose of calomel, the drinking of boiled water, and thorough protection against cold and wet."—Gwinn, 1902.

"If, as seems very probable and almost proved, the tick is the means by which the disease is spread, the question of the prevention of the disease resolves itself into the destruction of the tick. This is an almost impossible task over such a large area, especially of such varied topography. When conditions will permit, burning the undergrowth and stubble will be an effective method for the destruction of ticks. This may be done either in the early fall or, preferably, in the early spring, when the ticks are just beginning to move about."—Anderson, 1903c, p. 41.

"In view of the almost certain rôle of the tick in the conveyance of pyroplasmiasis to man, measures should be taken to reduce the numbers and limit the spread of this arachnid. The burning of underbrush, sawdust, etc., wherever practicable, is recommended. Persons going into the brush in the infected area should use all possible precautions to prevent ticks from biting them. As soon as a person is bitten by a tick, the arachnid should be removed and the wound cauterized by 95 per cent carbolic acid."—Wilson and Chowning, 1904a, p. 56.

Definite statements regarding prevention can not be made until the cause of the disease and its method of transmission are definitely known. All that can be said at present seems to be that people in the valley should take the best possible care of themselves during the spring months, and in case one member of a family is taken sick no other person should occupy the bed with the patient.

## SEQUELÆ.

*Idaho.*—Dubois (1896) states that no constitutional symptoms are left. The only sequela which Maxey (1899, p. 438) has noticed is a little stiffening of the knee joints, lasting some weeks.

Gates (1905, p. 115) reports endocarditis as sequela in his case 8.

One of the cases of 1903 had not fully regained the use of his legs in the summer of 1904.

#### AUTOPSIES.

The following autopsies have been made:

*Idaho*.—Apparently none.

*Montana*.—1897: Case 35, by Buckley, reported briefly in Wilson and Chowning, 1903a, page 33, and Anderson, 1903c, page 13. 1902: Case 89, by Wilson, Longeway, Brethauer, and Buckley, reported in Wilson and Chowning, 1903a, page 50; case 91, by Wilson, Brice, Longeway, and Buckley, reported in Wilson and Chowning, 1903a, page 52; case 93, by Wilson and Spottswood, reported in Wilson and Chowning, 1903a, page 54; case 94, by Wilson, Chowning, and Buckley, reported in Wilson and Chowning, 1903a, page 56; case 97, by Chowning, reported in Wilson and Chowning, 1903a, page 55; case 107, by Wilson and Longeway, reported in Wilson and Chowning, 1903a, page 47. 1903: Case 120, by Anderson, Wilson, Gwinn, Mills, Olson, Pixley, and Spottswood, reported in Anderson, 1903c, page 32. 1904: Case 11, by Ashburn, Mills, and Stiles, reported in Stiles, 1905, p. 109-110.

(?): Case —, by Hanbidge and Gwinn, reported briefly in Gwinn, 1902.

(?): Case —, briefly referred to by Gwinn, 1902.

#### PATHOLOGY.

*Idaho*.—"The pathological conditions, as at present understood, may be described with a large-sized interrogation point."—Maxey, 1899, pp. 434-435. Fairchild (1896) has seen no autopsies. The lesions, so far as Figgins (1896, p. 64) knows, are confined to the skin.

*Montana*.—Gwinn (1902) reports slight enlargement of the liver and kidneys, together with slight degeneration, in one case on autopsy.

The gross lesions are very uniform; intense rigor mortis appears early (Wilson and Chowning, 1904a, p. 41).

The changes are those which can be ascribed to interference with capillary circulation; the extravasation into and pigmentation of the skin account for the persistence of the spots for long periods after the recovery of the patients; there is acute parenchymatous degeneration of the heart muscles, spleen, liver, and kidney; the central nervous system is but little affected (Wilson and Chowning, 1904a, p. 43).

Anderson (1903c, p. 38) summarizes the post-mortem findings in 7 cases (6 of 1902, 1 of 1903) in the Bitter Root Valley.

Rigor mortis was intense in cases 89, 91, and 93 (Wilson and Chowning, 1903a, pp. 50, 52, 54), but not in case 120 (Anderson, 1903c, p. 32).

For further details see special organs.

#### CLINICAL HISTORIES.

During my work I did not take clinical notes, as I had so many other things to occupy my time. Clinical notes were, however, taken by the attending physicians and to some extent also by Doctor Ashburn. As both Wilson and Chowning (1902a, 1903a, 1904a) and Anderson (1903a, c) had studied the clinical side, and as I was looking especially for the life history of the parasite as a basis for prevention, I naturally neglected to go into an especially detailed clinical study, blood

counts, etc., such as I should have done had time permitted. Furthermore, some of the hospital charts became lost, so that part of the notes had to be written from memory or from brief memoranda.

#### BITTER ROOT VALLEY CASES, 1904.

*1904. Case 1.*—Attending physician, Doctor Buckley (notes written from memory later by Doctor Buckley: No microscopic examination of blood).

Male, age 66 years. Seen by Doctor Buckley, April 29, 1904. When first seen he had two wood-tick bites in the right inguinal region, each surrounded by an indurated inflammatory zone and showing an area of blackened skin about  $\frac{1}{2}$  inch in diameter at the center. Patient had frontal headache and general body aching. Temperature 102° F. Thought he had caught cold.

April 30, temperature 103°. Sclerotics much injected and face congested. Tongue moist. Pulse not high.

May 1, restless. No sleep night before. Bowels open. Temperature 103.5° F., a. m.: 104°, p. m. Mottling of skin noticed. Ecchymotic spots the size of a dollar seen on the abdomen. Scrotum black. That evening patient was feeling better and Doctor Buckley was telephoned he need not see him. May 2, worse. Spots dark purple. Temperature, a. m., 104°; p. m., 105°. Began to have delirium, which soon passed to coma, which lasted until death, on May 3, 1904.

*1904. Case 2.*—Attending physician, Dr. J. J. Buckley (notes written later by Doctor Ashburn from hospital chart and from statement by Doctor Buckley: Patient seen by Doctors Buckley, Ashburn, and Stiles; microscopic examination of dried blood from lips by Doctor Stiles, unsatisfactory).

Female, age 7 years 4 months. Born in Ravalli County, 15 miles south of present home.

Family history, negative.

Personal history (previous to present illness): Scarlatina in fall of 1903, mild. No other sickness.

Present illness: April 24, 1903, bitten back of ear by 3 ticks. Bites caused swelling next day. No discoloration: swelling was over upper part of sterno-mastoid, below bites. Had fever from that time on.

April 27, eruption showed on arms, shoulders, hips, knees, ankles, palms, and soles. Mother thought she had measles. She had also complained of sore eyes, some pain in back and head. Continued that way with increasing eruption and some darkening of it (browning) until May 2, when seen by Doctor McGrath and pronounced spotted fever. Brought to Missoula May 3. Complained of intense general soreness after appearance of eruption.

May 4: More irritation in throat. Very sore to the touch. Very drowsy. Cramps in stomach. Restless in afternoon.

May 5: Headache. Vomited twice. Sore throat. Very restless all night. Rash darker in color but not sore to the touch: patient very thirsty.

May 6: After sponging rested all forenoon, retained milk, some water, and all medicine. Throat much better. Not so thirsty as yesterday. Rested all afternoon. No vomiting. At 5 p. m., cramps in stomach.

May 7: Respiration a little more irregular: retains everything; apparently weaker, but pulse good: p. m., breathing very poor, but change for the better late in the



evening; breathing easy after a hot bath; slept calmly about two hours; became very restless again about 10.30 p. m.; pulse very poor at 12.

May 8: Choking spells about 12.30 a. m.; breathing very heavy; finally becomes unconscious; eyes bloodshot, pupils very much dilated; spots out in profusion; pulse good, but great struggle at times for breath.

May 9: Patient very restless during the night until about 3 a. m., then sank into a comatose condition; much weaker; spots very purple; p. m., sinking spell; improved after subcutaneous saline injection; lungs filling up; mouth full of bloody matter.

May 10: Finger nails turned purple, beginning at the tips about 1 a. m.; died with very little struggle at 1.25 o'clock a. m.

1904. *Case 3.*—Attending physician, Doctor Fitzgerald (notes prepared partially from hospital records, partially at bedside by Doctor Ashburn: patient seen and microscopic examination of fresh and stained blood by Doctors Fitzgerald, Buckley, Ashburn, and Stiles).

Female, age 28 years. Born in New Brunswick.

Family history: Father died of piles (?), one brother of consumption. Mother and four brothers and sisters living and well. History otherwise negative.

Personal history (previous to present illness): Had 3 children. Measles in childhood, bowel trouble last summer. No other sickness.

History previous to admission: Moved to present home in January. Had great fear of ticks and has watched for them and has not been bitten by them. Has had bites by chicken lice—last, probably about April 27. May 3 had chill. Backache and fever followed, and on May 7 eruption appeared on arms. Since that time, too, throat has been very sore.

Condition on admission: Date, May 10. First seen by Doctor Fitzgerald on May 7, 1904.

Symptoms: Sore throat, fever, slight malaise, but claims to feel well. Body presents on all parts a discrete maculo-papular eruption, very measly in appearance, but no crescentic arrangement. No purpura or petechiæ. Fauces and pharynx much injected and show adherent mucus-pus. Cervical glands enlarged. No eruption in mouth or throat. The tongue tremulous and has heavy, white, moist coat. Face placid. Blotched with eruptions. Eyes normal; mind clear. Heart sounds clear and regular. Lungs—Respiration slightly harsh and prolonged anteriorly; more so behind. Blowing over right upper lobe posteriorly. No cough. Spleen enlarged. Liver not enlarged. Abdomen not distended, tender, or painful. Menstruated April 11th. Bowels have been regular; now loose from salt enemata. Urine passed normally.

Diagnosis: Spotted fever.

Treatment: Seventh to 10th, calomel first day and quinine sulphate, grains 15, every 4 hours. Next day salol, grains 5, and quinine, grains 10, every 4 hours. Strychnine, grain,  $\frac{1}{16}$ , every 6 hours. Saline enema, 1 pint every 3 hours. Probably none of this was carried out as prescribed.

May 11: Arrived at Sisters Hospital this a. m. Nervous on admission. Looks and says she feels better. Throat not so sore. Spots unchanged, possibly a trifle darker. Not petechial. Skin presents faintest yellow tinge. No jaundice of sclerotics or tongue. Bowels moved after salt solution. Was very drowsy all afternoon; restless between 4 and 5 o'clock. Retained saline enemas. Patient apparently thirsty. Took nourishment; resting easy at 7.30 p. m.

May 12: At about 8 o'clock became drowsy; by 8.30 very stupid. Stupor continued all night with rapid respiration. Coma from 12 p. m. to 3 or 4 a. m. Bladder full at 3 a. m., when it was emptied for vesical irrigation. Now, 9.25 a. m., in deep sleep or coma. Pulse 80 and of good quality. Respiration 39 and slightly stertorous.

Blotches have disappeared from face and ordinary spots abundant there. Spots generally darkening. Now plum color, but not distinctly petechial. Lungs—Sounds very harsh all over front and back, with large coarse râles; 6 p. m., comatose all day; respiration rapid. Face dusky.

May 13: Quinine discontinued last night. Patient then comatose, breathing very rapidly and promised to die in a few hours, at most, as lungs were rapidly filling with fluid. This morning face darkly flushed, coma deep, great perspiration. Respiration will be for a time quiet and regular, for 5 or 10 minutes, and then very rapid (60) for a time. Spots no darker.

May 15: Filling of lungs progressed yesterday; edema well marked. Spots increased in size and darkened. Menstruation began for 1 hour yesterday and stopped. Began again last night and flowed freely until death. Urine and feces passed involuntarily and abundantly. Coughed freely yesterday. Finger nails this a. m. dark, face purple, much noise from breathing. Extremely offensive odor to breath. Dependent side of face turned black immediately after death, at 8 o'clock a. m. to-day.

*1904. Case 4.*—Attending physician, Doctor Merrick (notes prepared by Doctor Ashburn, from memoranda by Doctor Merrick; patient seen and microscopic examination of blood made by Doctors Merrick, Ashburn and Stiles).

Diagnosis: Spotted fever.

May 12. Symptoms: Severe intra-cranial and supra-orbital neuralgia, supra-scapular and lumbar pains. Tongue slightly furred and fissured. Anorexia. These symptoms dated from May 8, 1904. An eruption covering the legs to the knees.

May 13: The neuralgia considerably improved under codeine. The eruption increasing. Complains of illusions. Anorexia.

May 14: Eruption elevated and extended over trunk to face and arms. General condition prostrated. Pulse full. Blood examination for parasites negative.

May 15: Eruption dusky in morning, becomes brighter through the day, completely covers body and palms of hands. Complains of pains in head. Sleeplessness and illusions and weariness. Many red blood corpuscles are deformed. Blood examined by Doctor Ashburn.

May 16: Eruption possibly cleared. Patient feeling better; bowels moved freely. Temperature, 100; respiration, 20; pulse, 80. Anorexia and illusions persist, with prostration. Doctor Ashburn and Doctor Stiles made blood examination. No organisms were found.

May 17: Headache continues; fever 101.4. Illusions and prostration. No eruption on back, fading on arms and face. General condition of anxiety.

May 18: Headache relieved; condition improved. Eruption fading. Temperature, 100; pulse, 90. Sat in chair for one hour. Complains of weakness.

May 19: Temperature normal; pulse and respiration normal. Illusions disappear. Spots fading, only perceptible on limbs. Pains gone; tongue still coated; appetite returning.

May 21: Patient sitting up; weak and extremely nervous; spots about entirely faded away. Appetite improved and patient sleeps well. No anatomical lesions apparent.

N. B.—Doctor Merrick's note about the eruption covering the whole body evidently refers to its general distribution, as it was nowhere abundant, and was the lightest eruption occurring in any case this year.

*1904. Case 5.*—Attending physician, Doctor Mills (notes prepared by Doctor Ashburn; patient seen and microscopic examination of blood made by Doctors Mills, Ashburn, and Stiles).

Female; school-teacher; age 24 years; single.

Family history: Parents and brothers and sisters are living and in good health. No hereditary disease in family.

Personal history (previous to present illness): Measles in childhood. No other sickness. Been living at Woodman, in this county, since last September, teaching school. Kept house. No chickens. Just finished menstruating.

History previous to admission: Positive she has had no tick bites or other bites of any kind. Chill night of the 12th. Headache and fever continued then to present. Came here next day. Eruption appeared yesterday afternoon.

May 16. Symptoms: Quite calm facies; tongue has heavy, white, moist coat. Throat slightly sore, but shows no marked injection. No appetite. Bowels at present slightly constipated. Face slightly flushed. Spots on face, arms, hands, and body, etc. Heart sounds clear and regular. Breathing normal and sounds clear, front and back. Splenic dullness increased. Hepatic apparently diminished. Passing urine normally. Vomits practically everything taken by mouth. No nausea or pain in stomach. Headache present.

May 18: Condition good. Heart rapid and slightly weak and patient vomits a great deal, but otherwise is doing well. Bowels O. K. Patient slept well last night. Spots not brighter and seem to be fading. Mind clear. Headache improved.

May 23: Informed to-day by Doctor Mills that patient continued to do well until afternoon of May 21, when her respiration ceased. As heart was acting well, artificial respiration was resorted to. In five minutes patient breathed, roused, and was quite rational. Failure of respiration continued to occur at intervals, patient apparently forgetting to breathe. She died about 7 a. m. May 22. Hypodermics of morphine apparently acted as respiratory stimulant (Dr. Mills). Urine examined by Ashburn, passed May 18, contained albumen; reddish, yellow, turbid, acid, 1,028; no microscopic examination.

Later notes: Temperature on fourth day was 103° F. On day of death was 104° F. Treatment consisted principally of morphine in considerable doses. Diet was light, but almost everything was vomited unchanged soon after taking. This was also true of beer, which the patient had requested.

1904. Case 6.—Attending physician, Dr. Charles Pixley (patient seen and microscopic examination of blood made by Doctors Pixley, Mills, Ashburn, and Stiles).

REPORT OF A CASE OF SO-CALLED "SPOTTED FEVER" IN 1904. BY CHARLES  
PIXLEY, M. D.

Male patient, F. W., aged 21 years, of rather neurotic temperament. At one time he had used tobacco to excess. Two weeks prior to my first visit, which was on May 16, 1904, he had worked at Harvey Creek, a few miles east of Rock Creek, and parallel; also opposite to Quigley.

Patient was bitten by ticks at Harvey Creek; also at home at Missoula after his return. He had brought bedding home with him.

He had been complaining for about a week before I saw him. Two days prior to my visit he had fallen against the door at home, and he then went to bed. When first seen by me he had a temperature of 103° F., with headache, backache, and leg-ache; also felt restless. Small pink macular spots were present on legs, arms, and trunk; face of a florid complexion, but without visible spots.

May 16, p. m.: Temperature, 103; respiration rapid; pulse good, but rapid; nervous symptoms marked; restless; talk a little incoherent.

May 17, a. m.: Temperature, 102; nervous symptoms more marked; p. m., temperature rising until 9 p. m., 103.6; rash still more marked.



May 18, a. m. Temperature, 101.8: p. m., 103.8: restless, twitching of muscles, labored breathing, rash becoming purple and more plentiful.

May 19: Temperature about the same as on previous day: pulse weaker; extremely nervous, restless; respiration rapid and labored; delirious all the time; thrown into a state of tonus when touched lightly anywhere on the body.

May 20: All symptoms more marked; temperature about the same; rash profuse; delirium the most marked symptom; general rigidity of all parts of the body; twitching of face muscles; unable to swallow.

May 21: Died at 2.30 a. m., preceded by coma: temperature at 1 o'clock was 104.

Treatment was at first purging with calomel; continued use of calomel in  $\frac{1}{4}$ -grain doses every 4 hours, also inunction of blue ointment; quinine per mouth in 5-grain doses; whisky, strychnine, and morphine throughout the last 3 days.

The following additional notes on this case were made by Doctor Ashburn:

Personal history (previous to present illness): Working in lumber camp on Harvey Creek, where no spotted fever had previously been.

Present illness: Bitten by tick at Harvey Creek about May 5 (date not exact). Bitten again after coming home. May 13, taken sick with chill, fever, general pain, and aching. 14th, fell in door, sick. Seen by Doctor Pixley May 16. Temperature 103.5° F. Slightly delirious. Nervous twitchings and trembling. Spots beginning to appear on flanks and legs, unusually small. Temperature ranged higher in afternoon (to about 104°). Kept growing worse, twitching, tossing all the time. Spots increased gradually and darkened until at death patient had blue areas the size of the hand. Became more sensitive and irritable until at last the slightest touch would cause violent jump, almost a convulsion. Breathing irregular when awake, regular when sleeping. Had sore throat early and very slight nose bleed. Bowels O. K. Raving almost to time of death. Comatose for a few hours. Urine not examined. Physical examination negative except the skin. Rash when seen by me very fine.

Treatment: Calomel internally, mercurial inunctions. Quinine, 5 grains every 4 hours. Morphine as necessary. Formalin about 5 minims at end. Died Saturday night, May 21.

1904. *Case 7.*—Attending physician, Dr. J. W. Howard (patient seen also and microscopic examination made by Doctors McGrath, Ashburn, and Stiles).

REPORT OF A CASE OF SO-CALLED "SPOTTED FEVER" AT HAMILTON, 1904, BY  
DR. J. W. HOWARD.

G. M., male, aged 10 years, was brought to Hamilton from his home, 8 miles southwest of here, on the west side of the Bitter Root River. He came under my observation May 14, 1904.

The eruption at the time was very faintly marked, though he had been sick for 3 or 4 days: temperature, 103° F.; pulse, 110; very restless; appetite absent throughout entire sickness. Died May 22, 8 a. m.

The nose bled, not excessively, but frequently, for the last 5 days before death. The eruption was very backward and slow in coming out, and in fact never became pronounced. He had a convulsion 8 or 10 hours before death; do not know whether he had others later; during the convulsion he had slight opisthotonos. Disturbance of nervous system was marked throughout his illness by thrashing around in bed, rolling of the head, and throwing the arms; he could not be made to lie upon his left side for a minute at a time, but would immediately throw himself upon his right side or his back. Answered questions intelligently up to within a few hours of death.



Never complained of pain at any time, except occasionally when asked if his head ached, he would answer "Yes." Was seen by Doctors Ashburn and Stiles on May 20; they took blood samples for examination; examination negative; temperature ranged throughout from 97.5° to 105° F.; pulse from 85° to 125° per minute; bowels and urine both acted regularly and without assistance. The basis of treatment was quinine sulphate in large doses; other medication as indicated from time to time.

In addition to the above account I may give the following notes made by Doctor Ashburn:

Family history: Father killed. Mother alive and well. One sister died of whooping cough. One sister recovered from spotted fever under quinine 3 years ago.

Personal history (previous to present illness): Had chills and fever 6 years ago. Measles and whooping cough. No other sickness.

History previous to admission: May 11, complained at noon of being sick. Had nausea and headache. Slept that afternoon and was feverish and had headache and stomachache. On washing neck on first day complained of tenderness. May 13, spots showed on hips.

May 14, seen by Doctor Howard. Then stupid, restless. Temperature 103.5° F.; pulse, 115. Tongue had heavy moist coat. No pain except in bowels, from cathartic. No diarrhea, cough, or sore throat. After medicine, bowels loose. Has eaten practically nothing yet.

Physical signs: Temperature from 103° in evening to as low as 99° in morning. Vomiting more or less all through attack. Vomit greenish yellow.

Present condition, May 20: Expression dull. Very restless and tossing. Nauseated much of time. Nosebleed at times. Lips dry, blood stained, and crusted. Tongue dry, brown, and somewhat glazed. Vomit contains blood, thought to be from nose.

Eruption general, fine purplish. Less marked on face. Neck shows discoloration, yellowish. Heart sounds clear; respiration harsh, especially on right side. Spleen enlarged. Convulsions at 8 p. m., May 21. Died at 2 a. m., May 22. The daily dosage of quinine to May 20, was: 45, 45, 36, 48, 32, and 35 grains.

1904. *Case 8.*—Attending physician, Doctor Minshall; patient seen by Doctors Minshall, Gwinn, Ashburn, and Stiles; microscopic examination made by Ashburn and Stiles.

[Dr. Minshall's notes.]

Bitten by tick in 4 places Sunday night, May 15, 1904. Slight chill in afternoon of May 17. Was sick the following night and day. Was seen by Doctor Gwinn the evening of the 18th, who cauterized and dressed the tick bites. Temperature at that time said to have been 102. Severe headache, but no pain in back or limbs. I took charge of patient on May 19, at 5 o'clock p. m. Headache, but no pain elsewhere; coated tongue, intense thirst, but no nausea.

May 20: Condition much the same as yesterday, bowels moving freely.

May 21: No headache, no pain, no spots at 10 a. m., but skin presents a mottled appearance. At 2 p. m. spots appear quite distinctly on wrists and chest. By 5 p. m. all spots have disappeared. Skin of a decidedly mottled appearance.

Sunday, 22d: No change from yesterday. Appetite fairly good, mind clear, no pain in any part of the body.

Monday, 23d: No change since Saturday, except patient sleeps more, mind less active, some muttering during sleep.

Tuesday, 24th: Spots make appearance in decided manner over entire back, upper limbs, and chest. Nervous symptoms increase, more dullness, with slight delirium; in fact, sleeps most of time.

Wednesday, 25th: Eruption all over the body. Hyperesthesia of skin very marked. High nervous tension, muscles of back and limbs very rigid.

Thursday, 26th: Condition much the same as yesterday, with more or less coma.

Friday, 27th: Almost complete coma: all nervous symptoms increased.

Saturday, 28th: All conditions of two previous days more pronounced. A drink of water produces spasm of pharynx and diaphragm.

Sunday, 29th: Previous conditions more marked; slight edema of right lung noticed at 8 o'clock p. m.

Monday, 30th: Both lungs quite edematous. Remained in this condition during the day, dying at 9.15 o'clock p. m.

No photophobia at any time, pupils reacting to light up to and including 28th instant.

[Doctor Ashburn's notes.]

Tick bites. May 14: chill. 16th: fever, slight sore throat, and eruption on 23d.

May 26: Eruption profuse and measly everywhere but face. Temperature 103. Delirious. Tongue heavy, white coat, becoming dry and brown. Abdomen generally tender, especially right side. Hyperesthesia marked. Face flushed, conjunctivæ injected.

May 29: Comatose, spots purple, face still free. Respiration 50, pulse 138, temperature 103. Splenic dullness not obtainable.

May 30: Seen at 8.30 p. m. with Doctor Minshall and Doctor Stiles. Patient comatose. Lungs filled with fluid, so that loud rattling was heard throughout the room. Bubbling and crackling râles everywhere. Pulse weak, respiration 50. Patient evidently about to die, and decided to use bleeding followed by intravenous injection of 1:1000 formaline to normal salt solution. Patient died while this was being done. Informed by Doctor Minshall, nurse, and mother that reflex excitability had been so intense for 24 hours that slight touch used in putting spoon to lips, sponging, etc., would cause spasm and rigidity of whole body.

1904. *Case 9.*—Report on case "spotted fever" in 1904, by R. Gwinn, M. D.

G. C. T., of Florence, Mont., farmer, aged 32 years. Has been tick bitten every day or so for the whole spring; he has disinfected the bites with carbolic acid. On the 26th instant, was taken with chills, fever, and headache. Seen by Dr. J. F. Brice, of Stevensville, Mont., on 27th instant, who administered "calomel and fever medicine." Came to St. Patrick's Hospital at 4 p. m. to-day, when I find the patient complaining of headache and general soreness. Examination reveals many tick bites, together with an eruption all over like that of the "spotted fever." Pulse 92, temperature 103.2 under axilla. Pupils large. Respiration slightly accelerated. Tongue heavily coated. No apparent eruption in mouth or throat.

Diagnosis: The so-called "spotted fever."

May 29: Seems about the same. Pulse 100, temperature 103.2.

May 30: Patient much the same, except eruption darker and the skin and conjunctivæ more "jaundiced." Pulse 104, temperature 103.2. Doctors Mills and Stiles see the case with me, when a search of 1 hour by each of us for the parasite described by Doctors Wilson and Chowning is made with a negative result.

May 31, a. m.: Pulse 104, temperature in axilla 103.4; rested during latter part of night; injection of warm soapsuds causes good action of the bowels. Examination of eyes shows media a little blurred, so that the granular appearance of the retina can not be seen. The larger retinal blood vessels are quite plain, however; no swelling or blurring of disk; no hemorrhagic petechiæ in retina.

There is no stiffness of neck, and the head can readily be bent forward. No herpes. There is no pain complained of at all to-day; not even headache, and there was scarcely any yesterday.

May 31, p. m.: Pulse 122, axillary temperature 102.5, rectal temperature 104.8, respiration 28. Urine S. G. 1,022, acid, no sugar, trace of albumen, granular casts abundant, no blood. Patient's mind has been wandering for 2 days. Worse now.

June 1, a. m.: Pulse 120, rectal temperature 103.8 at 9 a. m. At 2 p. m., pulse 130, weak and irregular. At 8 p. m., pulse 120, rectal temperature 103.8; patient is delirious.

June 2, 9 a. m.: Pulse 130, weak and irregular; patient grew weaker and died at 8 p. m. from heart failure.

(The treatment in this case was symptomatic.)

The following additional notes were made by Doctor Ashburn:

Personal history (previous to present illness): Mumps, measles, scarlatina. No typhoid. Five years ago had spotted fever, which was aborted by Doctor Brice. Felt worse then at beginning than now. Did not have eruption.

History previous to admission: May 29: Been working in hills west of Florence all spring. Had very many tick bites which he cauterized with carbolic. May 25, had chill, followed by fever and mild pains. Took calomel. Headache more or less since, but not constant.

Condition on admission: May 28: Measly eruption, not thick, appeared about ankles. It now shows on ankles, face, and arms; possibly elsewhere, nowhere marked. Tongue white, moist, coated. Eyes suffused and light hurts them. Urinous (?) odor to breath. Bowels O. K. No cough, nose bleed, or especial discomfort. Urine passed about as usual. Spleen not demonstrably enlarged, not tender. Liver, heart, and lungs O. K. Abdomen not tender, shows eruption.

June 1: No photophobia, no pain. Apparent jaundice. Mind not so clear as at last note. Doctors Chowning, Stiles, and myself found nothing in blood.

1904. *Case 10.*—Attending physician. Doctor Mills (notes prepared by Doctor Ashburn; patient seen and microscopic examination of blood made by Doctors Mills, Ashburn, and Stiles).

J. B. Male, age 6 years. Had measles. Family history good.

Personal history (previous to present illness): Left Iowa 6 weeks ago. Been in Bozeman 5 weeks. June 2, arrived in Missoula and went on to Hamilton. Felt badly that night and ate no dinner. Ate none next day and vomited. Pain in abdomen, occiput, and back of neck, lasting to present, but now less marked. Fever. Seen by Doctor McGrath June 5, and eruption appeared June 6.

Symptoms: Bright and intelligent. Face flushed. Eyes injected, slightest convergent strabismus. Tongue white and moist. Cervical glands somewhat enlarged. Throat and mouth show no eruption or soreness. Some cough present. Spleen enlarged. Abdomen painful and tender. Measly eruption on hands, arms, feet, legs, and buttocks, palms, and soles. Pain and tenderness in abdomen, occiput, and neck. Bowels loose.

Blood examination: Fresh specimen negative. Large diplococcus in stain, looking like contamination.

June 8: Taking calomel and paregoric; room darkened. Has slept much of the time. Free from pain in the neck. Still has it in abdomen. Harsh breathing over right lower lobe.

June 9: Not seen by me. Doctor Mills reports spinal tenderness again. Pain still in abdomen. Spots not darkened. Condition much the same.

June 10: Appearance excellent. Very slight convergent squint still present. Spots fading on legs and body, not on soles. Pain still present in neck and abdomen. Tongue lightly coated. Knee jerks normal. Mother states that last night he cried that his eye was turning out. She looked, and divergent squint (outward rotation of



left eye) was present. She calmed him to sleep and the outward rotation was not present this morning.

June 12: Still complaining somewhat of pain in neck and belly. Spots fading. Doing well.

June 15: Pain in knees; temperature normal. Patient sitting up in bed and eating well. Spots all disappeared, but a few discernible on palms.

June 17: Patient left hospital practically well.

1904. *Case 11.*—Attending physician, Doctor Mills (notes prepared by Doctor Ashburn from hospital chart and bedside; patient seen and microscopic examination made by Doctors Mills, Ashburn, and Stiles).

Monday, June 20, 1904: Mrs. E., aged 23 years, married, one 9-months-old child living. Now pregnant in the sixth month. Patient born in the Tyrol, Austria, and arrived in this country 4 weeks ago. Came to Missoula 19 days ago. Remained in town 5 days and removed to a ranch purchased on the Lo Lo.

Saturday evening, June 18: Patient felt entirely well. That day she had merely tasted and then refused to eat veal because of bad odor. She had gone barefooted during the day and felt chilly, but it was a very cold day. That night she had occipital headache and could not sleep.

Sunday, the 19th: She vomited. All day she ate nothing and felt feverish. At 9.30 p. m. she started for Missoula, reaching here at 1 a. m. Slept at a hotel and came to hospital this morning. On her way to town she vomited bitter fluid. At present she has frontal headache, some tenderness of the back of the neck. Many abrasions on the feet and legs, all said to be due to scratching mosquito bites. Tick bites denied. Eyes slightly injected, otherwise normal. No tenderness of eyeballs, scalp, or general surface. Tongue moist and shows a moderate white coating. No eruption. Spleen not demonstrably enlarged and not tender. Bowels regular. Temperature, 101° F.; pulse, 105. Patient has had a slight cough for 2 weeks. Examination of lungs negative. Heart sounds normal.

June 22: Condition not so good. Pulse more rapid. Scattered measly eruption on body and limbs. Examination of the blood shows no protozoa. Leukocyte count 15,600.

June 23: Spleen not demonstrably enlarged. Fetal movements felt. Examination of lungs shows decidedly harsh respiratory sounds over the left apex anteriorly and posteriorly and over entire right lung posteriorly. Tongue red and moist, with white streaks. Eruption abundant on body, limbs, and face; measly, not petechial. Urinous (?) odor of breath.

June 24: Had respiratory depression last night, respiration falling to 8. Fetal movements felt at noon today. Spinal puncture made at 4.30 p. m., negative. Patient's general condition not so good as yesterday. Face somewhat dusky, spots darker, but not hemorrhagic. Sordes on lips and tongue. Patient very nervous. Urine, reddish-yellow, turbid; heavy yellowish precipitate; acid, specific gravity 1,018; albumen present in small amount; no sugar; no bile (Gmelin); urea, 3.5 per cent; abundant vaginal epithelium and small round epithelium; numerous blood, epithelial, and granular casts; free red and white blood cells; much granular debris.

June 25: Condition worse. Delirium constant and marked. Only 6 ounces of urine past 24 hours. Drawn by catheter. No fetal movements felt. Pulse very rapid and weak. Cyanosis present.

June 26: Miscarriage at 2 a. m. Very rapid and not followed by much bleeding. Child lived an hour and showed no spots. Patient very restless and constantly delirious; at times violent. Alcohol seems to aggravate this. Face cyanosed, spots purple and somewhat increased in size. Urine, 8 ounces in past 24 hours.

June 27: Patient was bled last evening to the amount of 12 ounces, with marked



temporary improvement; good night's rest followed. This morning restless and very delirious. Resists all attempts at passive motion. Urine passed involuntarily. Pupils widely dilated notwithstanding the administration of large amounts of morphine. Yesterday had 9 grains between 2 and 10 p. m. Face and spots not so dusky as yesterday. Lungs examined anteriorly and found as at last note. Harsh sounds at right apex.

June 28: Bled 1 ounce last night. Very restless and delirious this morning. Morphine, grains 4.5 from 7 to 10 a. m., with no apparent effect. Lungs edematous. Patient died at 11.30 o'clock a. m.

Autopsy, 3 hours after death: Body of well-nourished woman, showing no marks of violence except some small scabbed abrasions on the leg, phlebotomy incision on arm, and needle puncture below left breast and on arms. Purple discoloration on dependent portions of body. All measly eruption has disappeared from the upper portion of body. Posterior of body blue, shows many spots, very dark blue or purple, from 1 to 3 or 4 mm. in diameter. Over the left buttock and coccyx are a few purple areas (1 by 4 to 6 cm.) that look like extravasations. Slight bloody discharge from the vagina. Calvarium being removed shows outer surface of dura injected, but otherwise normal. Removal of dura shows some adhesions at the vertex between the membranes and the brain substance. Area of adhesions small. Veins on surface of brain are distended with blood. No pus or lymph seen. Base of skull and dura normal. Ventricles opened and appear normal, except for some distension of the veins. Small amount of bloody serum, blood of which very probably came from cut veins, in one lateral ventricle. Cerebrum on section appears about normal. Basal ganglia on section appear normal. Section of medulla, pons, and cerebellum shows nothing abnormal. Incision from manubrium to pubis shows good amount of subcutaneous fat. Muscles well developed and of good color. Peritoneum normal. Removal of sternum shows remnants of thymus gland. Pleural cavities normal, except a few adhesions between the left lung and the pericardium; latter contains an apparant excess of clear straw-colored serum. Heart distended with blood. Left ventricle partially contracted. Removal of right lung shows it lead color on upper surface, very dark posteriorly. Several dark spots one-eighth inch in diameter, apparently old, anteriorly. Entire lung edematous. Posterior portion extremely congested; in a condition of hypostatic pneumonia, and sinks in water. Bronchial glands enlarged and black. Removal of left lung shows same appearance as right except the pneumonic area is less marked and less extensive. Heart on removal seems normal, muscle well nourished; left side contains chicken fat and red clots. Valves normal. Right side contains a few small clots, white and red. Valves apparently normal. First part of aorta normal. Arch of aorta seems unusually small, just permitting little finger to enter. Examination of abdomen shows peritoneum normal, considerable amount of straw-colored serum present. Organs in normal relation and position. Spleen enlarged and bound down by posterior adhesions and adhesions to stomach. Soft, easily torn; slaty-purple in color. Liver apparently somewhat enlarged; paler than usual, with yellowish tinge, which is probably fat. Section of liver is decidedly pale; what little blood flows is also very pale; tissue is firm, though not apparently fibroid. Gall bladder distended with fluid bile, duct patulous. No gallstones. Gross appearance of left suprarenal shows it apparently normal. Size of left kidney 13 by 7 by 6 cm. Section shows the cortex little if at all altered. Capsule is adherent, carrying substance in removal. Areas of distinct pallor scattered over the surface. Right suprarenal appears congested, otherwise normal. Right kidney 12 by 7 cm. Cortex pale and thickened. (Doctor Mills thinks it normal.) Capsule adherent in same way. Pancreas apparently normal. Stomach shows injection about cardiac end, otherwise appears normal. Intestines removed, opened, and washed. Upper portion appears normal. Solitary glands and Peyer's patches appear somewhat swollen. Cecum shows considerable injection, which continues more or less throughout the colon. The uterus is enlarged

to the size of 2 fists and measures 11 cm. broad by 13 cm. long; soft, normal in appearance for a recently delivered uterus. The left ovary normal, as is the right, which contains corpus luteum. On section womb appears normal. Aspiration of spinal canal through the lumbar region withdrew 15 c. c. clear spinal fluid. Dura apparently normal. Spinal cord removed. On removing dura from cord showed considerable injection of vessels, which was probably hypostatic. No lymph exudation or other evidence of inflammation. Cross section of the cord at 1-inch intervals shows nothing abnormal. No scales present and organs could not be weighed.

The following notes have been sent to me by Dr. R. D. Alton, of Livingston, Mont.:

1904: (?) Case 12.—R. S., age 71, United States, came to St. Lukes Hospital, having been sent to me with the diagnosis "spotted fever."

Upon admission, May 14, 1904, he stated that he noticed 4 ticks in the vicinity of the left elbow, about 10 days ago.

Upon closely questioning him, stated he saw the ticks 11 days ago, or on the 3d of May. He further said he saw the rash on the body a few days after observing the ticks; that the arm "swelled up as large as two arms and was as red as a beet."

From the arm the rash spread all over the body. He is positive regarding the presence of the ticks. He is equally positive that he was not bitten by anything else. Upon removing his clothing the odor of the body led me to ask him if he had ever had measles, to which he replied, yes.

Temperature on admission was 102° F. This gradually declined to normal.

At no time was he delirious. He complained of great soreness all over the body; his feet were exquisitely tender and continued so until he left the hospital, May 27, 1904.

The urine on admission was scanty and highly colored, no sugar or albumen found. His diet while in the hospital consisted of fruits, vegetables, buttermilk, lemonade, etc.

He was given a combination of equal parts of Pulv. Glycyrrhizæ Comp. and Potassium Bitart., in water, to regulate the bowels, with Basham's Mixture after meals. In addition, he was given sour Rhine wine during the day.

He made an uneventful recovery, the rash disappearing from the face, forehead, trunk, arms, body, and lower extremities in the order named.

On the 25th of May his daughter called on him; from her I learned that measles were present in the vicinity from which he came—Lewiston, Meagher County, Mont.

The history, together with your negative findings, lead me to believe it was practically a case of measles, occurring in an old, poorly nourished, scorbutic patient.

1904: (?) Case 13.—On Sunday, June 12, 1904, I saw Charles E., age 26, United States, at Gardiner, Park County, Mont.

Upon examination found a cicatrix on the inner aspect of the left leg, middle third. Was told he had been bitten by a tick, 12 days previously.

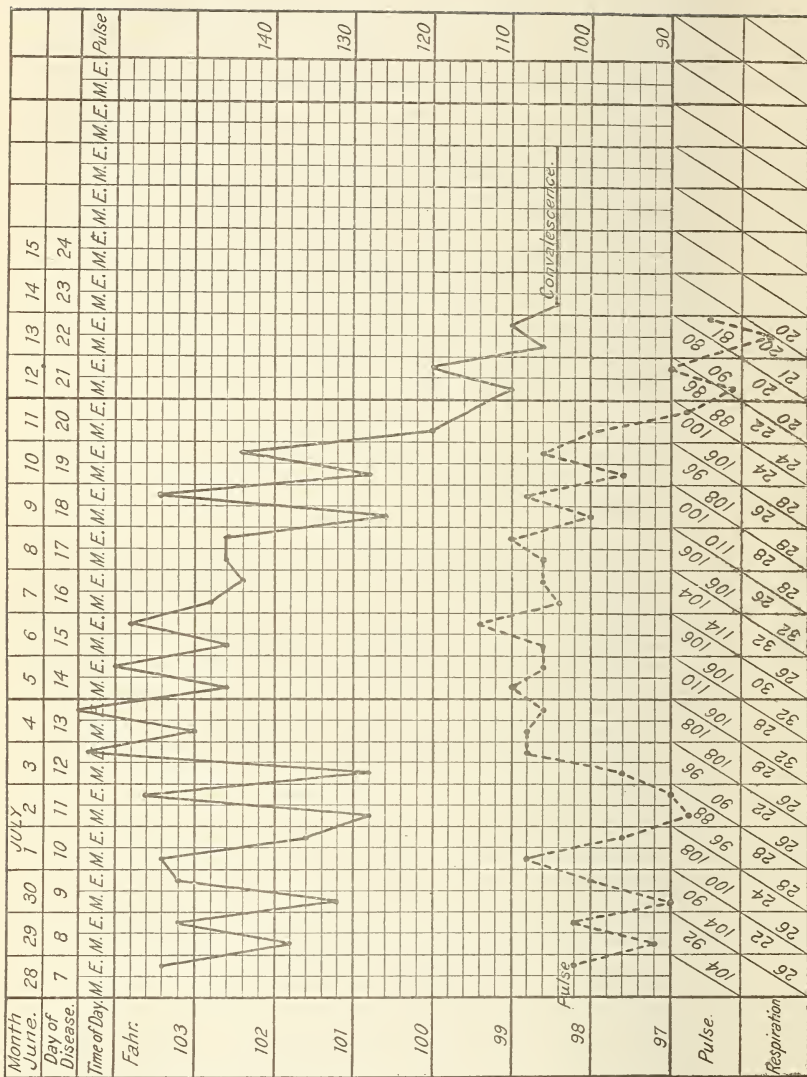
At the time of my visit he was delirious, picking at the bed clothing, muttering, and rolling restlessly from side to side. Pupils dilated and irresponsive to light, patellar tendon reflex exaggerated, ankle clonus pronounced. Tongue furred, bowels constipated, urine scanty and high colored. No albumen or sugar, Sp. gr. 1030. Temperature in axilla at 5.41 p. m., 104° F.

Ordered Sod. Bromide, grains xv, every 3 hours to produce rest, ice bags to head, and a hot, mustard, footbath.

While preparing to catheterize, he passed a fair quantity of urine, involuntarily. Further ordered he be given a glass of water every hour, with a glass of equal parts milk and water, every 4 hours. I inclose specimens of blood taken June 13, 1904.

On the 13th was informed by telephone that he had rested well, nervous symptoms







abating, kidneys acting freely, bowels moved from an enema given on the evening of the 12th June.

On the 14th improvement continued, temperature at 5.30 p. m., 102° F.

This may be a case of meningeal irritation following measles, or may be due to the tick bite and infection from that source.

I might mention that there was no cough or conjunctival congestion.

A CLINICAL REPORT OF FOUR CASES OF PIROPLASMOSIS HOMINIS, WITH TABLE OF SEVENTEEN CASES SEEN BY THE AUTHOR, BY L. A. GATES, M. D., BRIDGER, MONT.

*Case 11.*—C. B.; age, 26; male; occupation, ranchman; residence, Sage Creek, 20 miles southeast of Bridger, Mont. I saw this patient first July 1, 1903, being the tenth day of the disease. Patient gives a history of having been bitten by a tick June 21 on the left leg, 7 inches below the knee. The small wound caused by the bite became very sore, and there gradually developed around it an irregular, oblong dark bluish-red spot. The patient also states that he was bitten by a tick on the 22d and 23d, but only the first bite became sore.

On the 24th he had a very severe chill and says he has had considerable fever since that time; says he has been unable to sleep at all or eat anything for the past three days. Following the chill, a very severe headache came on, followed by severe aching of all of the skeletal muscles. He said "They ache like the toothache," being especially severe in the calves of the legs. On the 27th he vomited; on the 28th he noticed a few red spots on the palms of his hands, which he said seemed to be just under the skin and looked like the eruption of the measles. There were also, at this time, a few spots beginning to appear on the feet.

On examination this tenth day of the disease, we find the patient's countenance bears a look of nervous anxiety. The eyes are bright, with considerable congestion of the conjunctiva, the tongue quivers very much when protruded and is loaded with a heavy, dirty, brown coat; sides of the tongue are so livid as to be almost blue. A petechial eruption is seen in the skin and involves every portion from the soles of the feet to and including the scalp. They vary in color from bright red to bluish red. The greater number are seen on the extremities, where in places, two or more, by coalescence, form irregularly shaped spots. They vary in size from a pin head to the size of a dime, the larger ones being very irregular in outline. The skin is very dry.

There is some cough and on auscultation numerous dry rales are heard over the posterior portion of both lungs. The abdomen is moderately tympanitic. The urine, which is almost brown in color and lessened in amount, contains some albumen. The pulse is 104, weak and irregular, temperature, 103° F. The accompanying chart shows the temperature, pulse, and respiration from the seventh to the twenty-third day of the disease, at which time the patient was convalescent. On the eleventh day the patient was unable to urinate and the catheter was passed—urine very dark. The general course of the disease was severe in this case from the onset, though no complications occurred. Especially well marked was the cough and insomnia. The temperature touched normal on the twenty-third day, from which time the patient made rapid progress to complete recovery.

*Case 14.*—C. F. P.; male; age, 41 years; occupation, ranchman; residence, 4 miles southwest of Bridger, Mont. This patient was bitten on the leg by a tick April 11. On the 18th he felt a general soreness all over the body, which has gradually increased up to the first time I saw him, April 23. On the 21st he had a chill, followed by loss of appetite, headache, backache, and fever.

Examination: The face was slightly flushed, eyes dull, conjunctiva slightly injected, tongue has a grayish coat, bowels are constipated. There is an annoying, dry cough. No abnormal sounds on auscultation of the lungs; heart sounds normal; pulse rate, 70, strong and regular. The urine is high colored, but contains no albumen. Small

petechiæ are present over the entire body except the face. There is great muscular soreness, including the muscles of the eye. Has slept but little the last 2 or 3 nights. Temperature,  $102\frac{2}{3}^{\circ}$  F.

April 24: Patient feels better, eruption is not so well marked. He had a chill this a. m.; temperature,  $102^{\circ}$  F.; pulse, 64.

April 25: Patient complains bitterly of backache and pain in ankles and knee joints; temperature,  $103^{\circ}$  F.; pulse, 64.

April 26: Patient has had two chills this a. m.; anorexia complete; says he feels very tired; temperature,  $102\frac{2}{3}^{\circ}$  F.; pulse, 72.

April 27: Bowels moved twice during last 24 hours without laxative or enema. The cough is not so troublesome; the eyes are very sensitive to light; the spots are very conspicuous; temperature,  $101\frac{2}{3}^{\circ}$  F.; pulse, 62, full and regular.

April 28: Complains of frontal headache and severe, heavy, aching pains in the tibiæ; the spots are very red; the insomnia persists; temperature,  $103^{\circ}$  F.; pulse, 70.

April 29: Patient has had a slight chill this a. m.; the pain has left the legs; the eruption shows very bright and red; bowels loose; urine much reduced in quantity, no albumen; temperature,  $102.7^{\circ}$  F., pulse, 66.

May 1: Patient says he feels very much better; free from all muscular soreness and pain; slept fairly well last night; has some desire for food; the spots appear very dark red; temperature,  $101.5^{\circ}$  F.; pulse, 70. From this date the patient gradually recovered strength and was able to resume his work about the ranch June 1. This case was below average in severity for cases occurring in this valley. Of special interest in connection with this case are the slow pulse and repeated chills.

The following facts, I believe, are unique as regards the theory of the tick-bite origin of the disease, being, so far as I am aware, the only recorded instance in which a tick, after having bitten a patient suffering from "spotted fever" has then become detached from the patient, bitten a second person, and this second individual thereby contracting the disease. This is what actually occurred. The second party developed the disease in its most severe type, ending in death. (See p. 113.)

On May 29, Mr. C. A. H., of Bridger, Mont., visited the Clarke Fork Canyon, some 60 miles south of this place. He remained in the vicinity of the canyon about 4 days and while there was bitten in 5 or 6 places by ticks. About 7 days from the time he was first bitten by the ticks, viz, June 5, he arrived at his home in Bridger, at which time he felt the first symptoms of the onset of the disease. When he arrived home there were two ticks attached to his body which of their own accord, or from friction of the clothes, became detached from the body on June 6 and then bit his wife, who, on June 12—that is, after a period of incubation of 6 days—developed the first symptoms which marked the first symptoms of the disease. The petechiæ occurred on the 3d day. The following is a rather meager clinical history of the disease as it occurred in husband and wife.

*Case 15.*—C. A. H., male, age 46; occupation, stockman; residence, Bridger, Mont.

June 10: The patient is a large man, weighing about 198 pounds; has indulged very freely in alcoholics the past 3 years; has never been sick excepting 2 years ago, when he had smallpox. On the legs and abdomen are the marks of several tick bites, one of them on the ankle being very tender and around it a dark, bluish spot. There are now a number of small petechial spots on feet and hands, this being the fourth or fifth day since the onset. The conjunctivæ are congested, temperature  $103\frac{2}{3}^{\circ}$  F., pulse 97. He complains of general muscular soreness, severe backache, headache, and of being very tired and exhausted. No appetite whatever. Bowels are constipated, urine dark and shows a trace of albumen. During the course of the disease, which lasted 20 days in this case, the dry cough was most troublesome. Nervous symptoms were not marked. The urine was much lessened at times; besides a slight amount of albumen, it contained numerous blood and epithelial

casts. The spots appeared over the entire surface, being large and irregular on the legs, very bright red at the height of the disease, fading to a brownish pink color as the fever subsided. Many spots were yet visible 6 weeks after the temperature reached normal. Highest temperature observed was 104.1° F. The insomnia in this case was not troublesome. A severe intercostal neuralgia occurred during convalescence.

*Case 16.*—Mrs. G. H. (wife of C. A. H., case 15), age, 43; housewife; residence, Bridger, Mont. This patient is a very fleshy woman, with pendulous abdomen. She received bites from two ticks, which had previously bitten case 15, during the onset of the disease in that case. This occurred June 6. One tick bit this patient on the abdomen in the hypogastric region; the other on the leg. The bites occurred during the night; the ticks were removed and killed by the patient the following morning. Following the removal of the ticks she applied carbolic acid to the bites. On the evening of the 11th she felt chilly, feverish, and general malaise. The morning of the 12th she arose as usual, but had a pronounced rigor and such severe headache and aching in limbs and back as to compel her to return to bed. The temperature that evening rose to 104° F. During the first 12 days of the disease it ranged between 102° and 104.4° F., for 5 days keeping close to the 104° F. mark. After the twelfth day of the disease the temperature gradually fell and the eighteenth day it registered 97° F., when an unfavorable prognosis was given, though in every other way the patient seemed on the road to recovery. The following four days the temperature remained about normal.

The respirations, early in the course of the disease, reached 40 per minute, at which rate they remained until the last week of the disease. Cheyne-Stokes respiration was observed during the last of the second week, some cough, but not so much as is usually observed. The heart action was weak from the first, and during the second and third weeks became very weak and irregular, with very low arterial pressure. The rate of pulsation varied from 120 to 140 per minute. The tongue, mouth, and pharynx became very dry early in the disease. No vomiting occurred, and food was well taken at all times. The urine became very scant at the end of the first week and contained many fatty, blood, and epithelial casts and, at times, some albumen. By the end of the second week the urine had increased to normal amount and was free from albumen and casts. The intensity with which the disease attacked the nervous system was marked from the onset. A low, muttering delirium came on during first week. During the second week patient was in heavy stupor from which she could be aroused with difficulty, but when aroused would answer questions correctly and then perhaps talk at random. The condition of the mind approached the normal during the third week. The eyes were very sensitive to light and very much congested. The petechiæ commenced to appear on the third day, first on feet, ankles, hands, and wrists. It rapidly spread all over the body and was very thickly distributed on the back. During the third week the patient each day expressed herself as feeling better than on the day previous. The temperature, after having reached 97° F., became normal. The respiration was easier and all symptoms seemed to indicate a beginning convalescence. On the twenty-second day of the disease the patient said to the nurse, "I feel a pain around my heart." The nurse turned her on her side, in which position she seemed to rest a few minutes and then breathed her last.

The points of interest in this case were mode of infection (see also, p. 23); high temperature at onset, which persisted; rapid breathing; great congestion of the kidneys; extreme weakness of heart action; the decided effect on the nervous system; subnormal temperature, and sudden death without warning, when apparently recovering from the disease.

No. case.	Year.	Date on set.	Patient's initials.	Residence.	Sex.	Age.	Occupation.	Eruption appeared.
1	1894	June ...	C. G . . . . .	Myersville, Wyo. . . . .	Male ...	Yrs. 5	.....	Second or third day.
2	1898	May 24..	L. M. . . . .	Thermopolis, Wyo. . . . .	.....do ...	23	Ranch hand.	Fourth day.
3	1898	June ...	D. W. . . . .	.....do . . . . .	.....do ...	47	Freighter....	No record ..
4	1900	April ...	.....	7 miles SE. Bridger, Mont.	.....do ...	29	Sheep herder	.....do .....
5	1900	April 17.	E. G . . . . .	1 mile SE. Bridger, Mont.	Female.	6	.....	Fourth day..
6	1900	April 15.	J. A. . . . .	.....do . . . . .	Male ...	39	Ranch hand.	Third or fourth day.
7	1901	May ...	.....	Shoshone River, Wyo. . . . .	.....do ...	52	Ranchman ..	No record ..
8	1902	May 15..	W. S. . . . .	South of Bridger, Mont.	.....do ...	31	Trapper .....	Fifth day...
9	1902	May ...	A. W . . . . .	Near Bridger, Mont. . . . .	Female.	8	.....	No record ..
10	1903	May 9...	M. H . . . . .	7 miles SW. Bridger, Mont.	.....do ...	67	Nurse .....	Sixth day...
11	1903	June 21.	C. B . . . . .	Sage Creek, 25 miles SE. Bridger, Mont.	Male ...	26	Ranchman ..	Fifth day...
12	1903	June 9..	H. L. . . . .	5 miles SE. Bridger, Mont.	Female.	47	Housewife...	Fourth day.
13	1903	June 5..	W. C. . . . .	10 miles SW. Bridger, Mont.	Male ...	6	.....	No record ..
14	1904	April 18.	C. F. P. . . . .	4 miles SW. Bridger, Mont.	.....do ...	41	Ranchman ..	Fourth day.
15	1904	June 5..	C. A. H. . . . .	Bridger, Mont. . . . .	.....do ...	46	Stockman ...	Fifth day...
16	1904	June 12.	Mrs. G. H. . . . .	.....do . . . . .	Female.	43	Housewife...	Third day ..
17	1904	May 9...	J. N . . . . .	2 miles N. Bridger, Mont.	Male ...	45	Ranchman ..	Fourth day.



Date of tick bite and location.	Death or convalescence.	Remarks.
No history of bite, but was much exposed.	Convalescence after 10 days..	This was a very mild case, as is always the case in children, so far as my observations go.
.....do .....	Convalescence after 21 days..	A very severe, though uncomplicated case. The petechiæ coalescing to form great irregular spots, which could still be seen 4 months after recovery.
.....do .....	Convalescence after 3½ weeks.	This man did not call a physician, and took no medicine. The spots were very large and bright.
Was bitten, date not known..	Was in bed but a few days ...	This man came to the office with eruption well developed. Was not seen again by me.
No history of bite, but was out among the sagebrush every day, and so very much exposed to ticks.	Convalescence after — days..	Mild case, few spots, not petechial in character.
.....do .....	Died the twenty-ninth day of the disease.	This is the most severe case I have seen. Spots were large and on the legs became black and gangrenous before death. The skin on the scrotum was also gangrenous. Very deep stupor for 10 days before death.
Bitten on leg .....	Slow recovery after 4 weeks..	Spots could be seen 4 months after recovery. Delirious 2 weeks.
Bitten several places .....	Recovery after 18 days .....	Severe case. Endocarditis as sequela.
No record; exposed .....	Did not remain ill in bed for 2 weeks.	Very mild. Slight fever, general malaise, eruption rose color, not petechial.
Bitten on leg and thigh May 4 and 8.	Died on eighth day of the disease.	Severe parenchymatous inflammation of kidneys.
Bitten on leg June 15, 16, and 17.	Recovery after 22 days .....	Type of disease severe. No after effects.
Bitten several places during first week of June.	Slow recovery after 20 days ..	Kidneys suffered especially.
Bitten on back of head; no date.	Convalescent twelfth day ....	This little patient was seen by me but once, and was in bed about 8 or 10 days.
Bitten on leg April 11 .....	Recovery after 12 days .....	Disease was of medium severity. Pulse never above 70. A greater part of the time it was 64.
Several bites from May 30 to June 5 on legs and abdomen.	Convalescent twenty-second day.	Case from which ticks became detached, and then bit wife of patient, thereby infecting her.
Bitten on leg and abdomen by ticks from case 15.	Died on twenty-second day of disease.	This case was bitten by ticks from case 15, which had drawn blood from case 15 during onset of disease.
No record .....	Convalescent fifteenth day...	This patient is much given to drink, and would not be likely to know whether or not a tick had bitten him. This case was certainly as spotted as could be.

## A POSSIBLE CASE OF "SPOTTED FEVER" IN UTAH, BY R. J. SMITH, M. D.

[Personal letter, dated May 22, 1904, to Dr. Thomas D. Tuttle, secretary Montana State board of health.]

\* \* \* \* \*

I have a case that looks to me very much like wood-tick disease, "spotted fever."

The patient, female, age 24, was visiting in Idaho, where within 2 miles of the place she was visiting, there were 2 cases of "spotted fever," but I have been unable to obtain information as to onset, symptoms, etc. One young man recovered, left in very weak condition.

Ten days ago this patient of mine was bitten in four places by 2 ticks, the ticks penetrating the right leg below the knee.

The parts became very painful and swollen and in three or four days the patient suddenly became very ill, severe nausea, intense headache, backache, sore muscles, pains in limbs; could not sit up without dizziness and nausea; did not vomit.

Her mother brought her home on Friday; I was called Saturday, 21st, and found temperature 103.5°, pulse 92, eyes very bright, some roseolous spots on wrists, arms, back, abdomen, ankles; patient very nervous, stiff neck, no spinal tenderness, no hyperesthesia; numb all over, some twitching of muscles of forearm and legs. Temperature at 1.30 p. m., 103.5°; 4 p. m., 103°; 10 p. m., 103°; this (Sunday) a. m., 104°.

Temperature same all evening and night. Bathing had no effect. When face was first touched with cold water during the bathing chill came on; quite severe. No elevation of temperature afterwards.

This morning spots all over body, on palms and soles; not papular except here and there; look like the roseola of typhoid fever; no pain, no nervousness, slight hacking cough, nausea completely relieved, no tenderness over spine, an occasional pain in ankles, muscles without stiffness, neck freely movable, eyes very bright, urine free; temperature 104, pulse 98; bowels moved freely; slept well, no opiates used. Gave cicutine hydrobromate,  $\frac{1}{67}$  grain, every hour until pain and stiffness relieved last evening—4 doses removed pain, etc.

My diagnosis is held in abeyance.

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*Dr. Goldberger*

TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 21.

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# THE IMMUNITY UNIT

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# DIPHTHERIA ANTITOXIN

(BASED ON EHRlich'S NORMAL SERUM).

Official Standard prepared under the Act approved July 1, 1902.

BY

M. J. ROSENAU,  
DIRECTOR OF THE HYGIENIC LABORATORY.



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The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, located in Washington, was authorized by act of Congress, March 3, 1901.

The following *bulletins* [Bulls. Nos. 1-7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

- No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.
- No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.
- No. 3.—Sulphur dioxide as a germicidal agent. By H. D. Geddings.
- No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.
- No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.
- No. 6.—Disinfection against mosquitoes with formaldehyd and sulphur dioxid. By M. J. Rosenau.

No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.

By act of Congress, approved July 1, 1902, the name of the "United States Marine-Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.

Since the change of name of the Service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:

- No. 8.—Laboratory course in pathology and bacteriology. By M. J. Rosenau. (Revised edition March, 1904.)
- No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.
- No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchyllostomiasis) in the United States. By Ch. Wardell Stiles.
- No. 11.—An experimental investigation of *Trypanosoma lewisi*. By Edward Francis.

No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.

No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis*; by Ch. Wardell Stiles.

No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.

No. 15.—Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allan J. McLaughlin.

No. 16.—The antiseptic and germicidal properties of glycerin. By M. J. Rosenau.

No. 17.—Illustrated key to the trematode parasites of man. By Ch. Wardell Stiles.

No. 18.—An account of the tapeworms of the genus *Hymenolepis* parasitic in man, including reports of several new cases of the dwarf tapeworm (*H. nana*) in the United States. By Brayton H. Ransom.

TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 21.

APRIL, 1905.

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# THE IMMUNITY UNIT

FOR STANDARDIZING

# DIPHTHERIA ANTITOXIN

(BASED ON EHRlich'S NORMAL SERUM)

Official Standard prepared under the Act approved July 1, 1902.

BY

M. J. ROSENAU,

DIRECTOR OF THE HYGIENIC LABORATORY.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.

1905.

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*United States Public Health and Marine-Hospital Service.*

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## PREFACE.

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The object of this bulletin is to describe the methods by which the immunity unit for measuring the strength of diphtheria antitoxin is obtained, and the principles involved.

The unit is based on the one established by Ehrlich, and has been made by comparison with the normal serum sent to this laboratory by the Kgl. Pr. Institut für experimentelle Therapie, Frankfurt a. M., Germany.

On account of the technical difficulties met in testing the strength of diphtheria antitoxin, and the intricate composition of the diphtheria poison, as well as the peculiar chemical relations existing between the toxine and the antitoxin, it has been necessary to enter into the many details of every portion of the process in order that those who use this standard may do so under the same conditions. Otherwise comparable results would not be obtained.

In such an apparently simple procedure as measuring two pieces of metal, as is done in duplicating the standard meter and yard, the greatest attention to many details must be observed. It can therefore be well understood how important it is, in comparing a standard based upon the physiological action of a mixture of two complicated organic substances, not to neglect the smallest detail that would insure accuracy.

As the unit made in the Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service, is the legal unit for this country, the methods by which it is produced, as described in this bulletin, may be taken as official.

All standards are fundamentally arbitrary quantities. If all the meter bars or yardsticks were lost it would be difficult if not impossible to produce others having the exact lengths of the originals, which are therefore guarded against harm under conditions of uniform temperature, etc., to prevent changes in length.

The antidiphtheric serum that has been carefully standardized and is used as the unit of strength for the measurement of diphtheria antitoxin is similarly kept under strict conditions of light, heat, moisture, etc., in the Hygienic Laboratory, U. S. Public Health and

Marine-Hospital Service. From time to time duplicates of this serum will be made to guard against deterioration or accident to the original.

This standard serum is preserved in small tubes. Every two months one of these tubes is opened, tested, and distributed to the licensed manufacturers and others who are working in this line.

The particular object of this standard is to insure the strength of antidiphtheritic serum sold in the United States by licensed manufacturers.

In accordance with the act of Congress approved July 1, 1902, no one is allowed to engage in interstate traffic in antitoxin without a license issued by the Secretary of the Treasury on recommendation of the Surgeon-General of the Public Health and Marine-Hospital Service. This license is issued only after a careful inspection of the establishment, its methods of manufacture, and an examination of its products for purity and potency at the hygienic laboratory of this Service.

The strength of diphtheria antitoxin is expressed in units. As the question has often been asked, What is the unit for this country? it became the duty of the Public Health and Marine-Hospital Service to establish and maintain a standard of measurement in order to bring about uniformity among American manufacturers. There is also the advantage of guaranteeing to physicians and patients using this wonderful specific remedy for diphtheria the fact that they are employing a remedy of sufficient strength to protect or cure. Weak serums have been shown to be practically useless.

The very unfavorable results obtained in England in 1895 in the handling of diphtheria with serum were due, according to the report of the Lancet Commission (*Lancet*, July 19, 1896), in a great majority of cases to the use of serums too weak to produce therapeutic results.

Experimental researches, for example, the very careful work of Madsen, in Copenhagen, 1896, showed that for therapeutic purposes weak serum is of very little value.

The fact need not be emphasized, as Ehrlich pointed out long ago, that for the whole question of the cure and prophylaxis of diphtheria by a serum therapy, as well as for the purposes of scientific investigation, it is important to use an antitoxin whose value has been definitely ascertained.

### ACKNOWLEDGMENT.

As this standard is based upon the one established by Ehrlich, the principles involved and the methods employed are practically a reproduction of his work. First of all, I have to acknowledge not only the debt I individually owe, but the debt that all the world owes, to the remarkable genius of Ehrlich, who has done more, perhaps, to forward the problems of serum therapy than anyone else, not excepting Behring and Roux, the discoverers of the practical uses of diphtheria antitoxin. It is therefore evident that in the following pages no claim to originality can be made. In a few instances some improvements in the methods of testing, leading to increased accuracy, have been introduced. I have naturally drawn heavily upon the published literature on the subject, particularly the writings of Ehrlich, also Morgenroth, von Dungern, Madsen, Arrbenius, Marx, Smith, and Welch.

A bibliography of all the articles consulted in writing this bulletin, as well as in the work of standardizing the serum, will be found on page 85.

It is a pleasure to acknowledge particularly the assistance I have had from my colleague, Dr. Reid Hunt, Chief of the Division of Pharmacology, whose deep insight into physiological chemistry has helped me to a better understanding of some of the problems involved in making the immunity unit.

I also wish to acknowledge the assistance especially of Passed Assistant Surgeons John F. Anderson, the assistant director in this laboratory, and also Passed Assistant Surgeon R. von Ezdorf, and T. B. McClintic, and Assistant Surgeons Edward Francis and A. M. Stimson, who have faithfully carried out many details of the work under my supervision.

The inception of the law and the benefits that have already resulted from its administration are properly credited to the Surgeon-General of the Public Health and Marine-Hospital Service. It is therefore a pleasant duty to acknowledge this as one of the many debts our country owes to the public health work of Walter Wyman.





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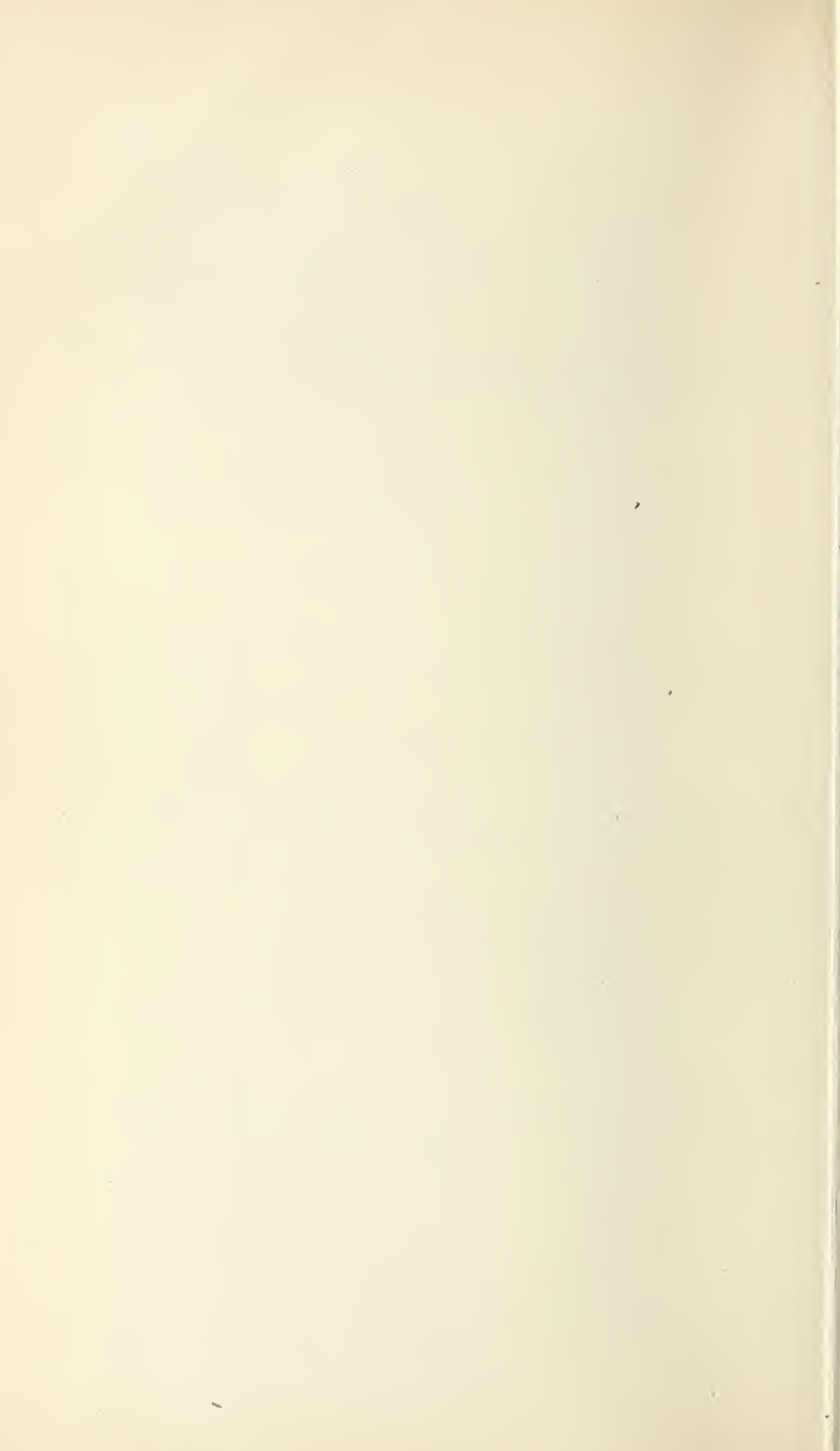
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# THE IMMUNITY UNIT FOR STANDARDIZING DIPHThERIA ANTITOXIN.

[Based on Ehrlich's normal serum. Official standard prepared under the act approved July 1, 1902.]

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By MILTON J. ROSENAU,

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

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## EHRlich's SIDE-CHAIN THEORY OF IMMUNITY.

Ehrlich's<sup>a</sup> side-chain theory is a brilliant chemical conception, giving the only satisfactory explanation of many of the phenomena concerned in immunity. In one sense it has been likened to Weigert's teachings of inflammation and the process of repair in so far that cognizance is taken of nature's prodigality. For instance, a much larger amount of material is thrown out than necessary to repair a wound. So, too, in antitoxic immunity a much larger amount of antitoxin is produced than necessary to neutralize the toxine.

In Ehrlich's conception the fundamental processes of immunity reside in the cells of the body. These cells are attacked by the poison and if not destroyed are stimulated into the overproduction of "antibodies" capable of combining with and neutralizing the poison.

Just what cells of the body play the most important rôle in the production of immunity is not exactly clear. It may be, as Ehrlich supposes, that this power resides in any organ or tissue.

In Metchnikoff's<sup>b</sup> theory of phagocytosis the free ameboid cells of the body play the all-important rôle. It is the macrophages and microphages seeking food that engulf and destroy the bacteria. In the process of digesting the bacteria the cell secretes the enzymelike substance which has the power of neutralizing the bacterial poisons.

It is surprising that the nutrition and metabolism of the cell lie at the foundation of two such divergent theories as Metchnikoff's and Ehrlich's.

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<sup>a</sup> Ehrlich: Die wertbemessung des diphtherieheilserums und deren theoretische grundlagen. *Klin. jahrb.*, Jena, v. 6 (2), 1897, pp. 299-326.

—— Ueber die constitution des diphtheriegiftes. *Deut. med. woch.*, Leipzig, v. 24 (38), 1898, pp. 597-600.

—— Croonian lecture. On immunity with special reference to cell life. *Proc. roy. soc.*, London, v. 66, pp. 424-448, pls. 6-7.

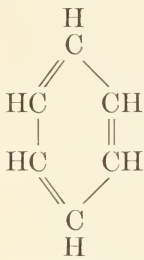
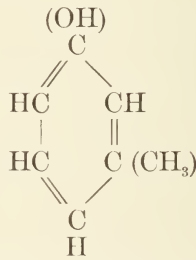
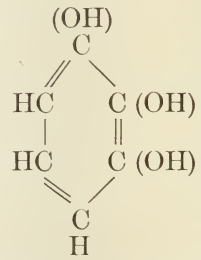
<sup>b</sup> Metchnikoff, Elie: *L'immunité dans les maladies infectieuses*. Paris, 1901. 45 figs., 600 pp.

According to the former it is the physical movements of the amoeboid cell searching for food which, by a process known as phagocytosis, takes the bacteria into its protoplasm, forms a digestive vacuole around it, and then excretes the enzymelike substances (cytase<sup>a</sup>) useful in protecting the organism against the soluble poison of the bacteria.

According to Ehrlich the hungry protoplasm of any cell, with its complicated molecule having side chains of various combining affinities ready to unite with suitable food molecules brought to it by the blood and body juices, lies at the foundation of his explanation of the chemical production of the antitoxin. It is strange that the same combining affinity should exist between the protoplasm of the cell and the proteid molecules that furnish it food as between the cell protoplasm and the toxins<sup>b</sup> of the bacterial poisons.

In considering Ehrlich's<sup>c</sup> side-chain theory it is necessary to disregard the microscopic structure of the cell and to think of the protoplasm as consisting of living molecules of extraordinary chemical complexity. The molecule of protoplasm has a central "nucleus" with "side chains," "lateral chains," or "bonds" of varying combining capacities. These "side chains" serve to bind the molecule to other molecules having proper combining affinities.

This arrangement of molecules with side chains is a well-known occurrence in organic compounds. The benzol ring forms one of the best and simplest examples.

Benzol C<sub>6</sub>H<sub>6</sub>Metaresol C<sub>6</sub>H<sub>4</sub> (CH<sub>3</sub>) (OH)Pyrogallic acid C<sub>6</sub>H<sub>3</sub> (OH)<sub>3</sub>

<sup>a</sup> Macrocytase, microcytase, philocytase.

<sup>b</sup> I have made a distinction in this bulletin between "toxine" and "toxin."

Some confusion arises in the literature for want of two words to represent two separate substances. The diphtheria poison contained in the toxic broth was first called "toxine," usually "toxin." It is now often spoken of as the "diphtheria poison." This filtered broth, containing a number of poisonous substances, I have called the toxine.

I have restricted the name "toxin" to the most important constituent of the toxine. The *toxin*, as will be found later, is only one of several allied poisons found in the toxine.

<sup>c</sup> Ehrlich: Die wertbemessung des diphtherieheiserums und deren theoretische grundlagen. Klin. jahrb., Jena, v. 6 (2), 1897, pp. 299-326.

By replacing one of the H atoms in the benzol ring with the methyl radical ( $\text{CH}_3$ ) we have toluol; by replacing one of the H atoms with the hydroxyl group (OH) we have phenol; by substituting two hydroxyl groups we have resorcin, etc.; three, pyrogallie acid, etc.; by substituting one hydrogen atom of the ring with the hydroxyl radical and another one with the methyl radical we have the cresols.

These simple illustrations from well known organic compounds illustrate the central molecular mass of atoms with its side chains and combining affinities, to which the molecule of protoplasm is likened.

In applying this analogy to the molecule of protoplasm the name "receptor" is given these side chains, or secondary atomic complexes of the molecular group. Contrary to the simple analogies above given each molecule of protoplasm has many different kinds of receptors, as shown by the schematic diagram in fig. 1a. These receptors have a specific affinity for the molecules of food, and also combine with the toxic molecules.

The *toxin* molecule, according to Ehrlich, consists of two important parts. One is known as the *toxophore group*, the other as the *haptophore group*.

The *toxophore group* of the toxin is that portion of the molecule which exerts a poisonous effect upon the protoplasm of the cell. This group is less stable than the haptophore

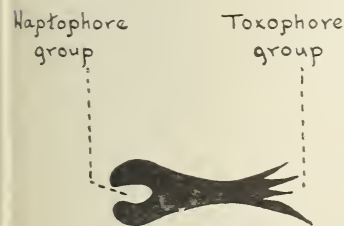


FIG. 1b.—The *toxin* molecule: showing the haptophore (combining) group, and the toxophore (poison) group.

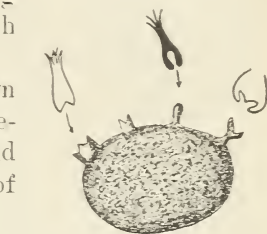


FIG. 1a.\*—The cell with its various combining groups or side chains, known as receptors. Various toxins are shown having specific affinity for the proper shaped receptors.

group. The *haptophore group* is the seizing or combining portion of the *toxin* molecule ( $\alpha\pi\tau\omega$ , to seize or attack). The haptophore group of the *toxins* have specific combining affinities for the receptors of certain cells, which in part explains the selective action of these poisons.

Toxines, such as diphtheria toxine, gradually diminish in toxicity, but retain the same power of chemical combination with the antitoxin. This phenomenon is explained by the formation of *toxoids*.

Ehrlich inferred the presence of the *toxoid* from the following simple experiment: He had a toxine which required 0.003 c. c. to kill a guinea pig. After nine months this poison weakened, so that it

\* FOOT NOTE.—Fig. 1a-i.—Diagrammatic representation of Ehrlich's side chain theory of immunity (Croonian Lecture, Proc. Royal Society of London, vol. 66, 1900, p. 437).

required three times as much; that is, 0.009 c. c. to kill a guinea pig. Nevertheless, the combining power of the toxine for antitoxin remained the same.

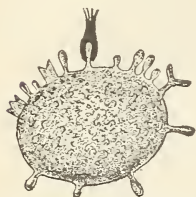


FIG. 1c.—The first stage of antitoxin formation; a toxin molecule anchored to a receptor.

*Toxoids* are altered *toxins*. They consist of the toxic molecule in which the toxophore group has been destroyed, leaving only the haptophore or combining group, which while able to satisfy the combining affinities of the antitoxin is no longer able to poison the protoplasm of the cell.

The diphtheria bacillus, during the process of its growth and multiplication in the body or in an artificial culture medium, produces several poisons, one of which is known as the diphtheria *toxin*. As above stated, the diphtheria *toxin* consists of a toxophore and haptophore group. In the body the latter unites chemically with the receptors of the cells. When this takes place one of two consequences may result: Either (1) the cell is so severely poisoned that it dies, or (2) the living molecule of protoplasm is stimulated so as to excite a defensive action by the reproduction of the receptors. Continued stimulation produced by the periodical injection of toxine results in an over production of receptors which finally loosen and float free in the blood serum and body juices.

Antitoxin consists of these free receptors floating in the blood serum. If now we introduce a liquid containing the *toxin* into the blood, it is immediately neutralized by combining with the free receptors through its haptophore group. All the combining affinities of the *toxin* are thus satisfied or saturated, so that the *toxin* is no longer able to unite with the receptors still attached to the cell, and this poison is thus rendered harmless.

It is of the greatest practical importance to know from what organs or tissues the receptors derive their origin.

It is by no means a necessary corollary of the side chain theory, as is often supposed, that the receptors are found only in those organs upon which the poisonous effects of a toxine are particularly manifested. On the contrary, Ehrlich and Morgenroth<sup>a</sup> believe that receptors capable of



FIG. 1d.—The second stage; continued stimulation causes a reproduction of receptors.

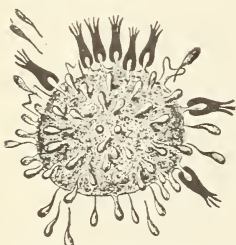


FIG. 1e.—Third stage; the receptors beginning to leave the cell.

<sup>a</sup> Ehrlich, P., & Morgenroth, J.: Wirkung und entstehung der aktiven stoffe im serum nach der seitenkettentheorie. Handbuch der pathogen mikroorganismen, W. Kolle and A. Wassermann, Jena, 1904.



combining with the toxine are produced in many different parts of the body, especially in tissues and organs having the power of anchoring the toxine without causing serious poisonous effects.

The connective tissue is believed to be especially rich in receptors, evidenced by the local reaction caused by the subcutaneous inoculation of diphtheria toxine, ricin, abrin, and similar poisons. In fact, one would not be far wrong in assigning a particular significance, in the production of receptors, to just those organs which show unimportant vital response, because in such tissues the injurious effects of the toxophore group are absent or of such diminished importance that the regenerative powers of such tissues are not retarded.

The presence or absence of receptors capable of binding the toxine, as well as their number and distribution, are factors which determine the susceptibility of different species of animals against the various toxins. These factors also determine the individual variations in the susceptibility to poisons and further explain the instances of natural immunity to toxins.

An example is given by Sachs,<sup>a</sup> who studied the reaction of guinea-pig blood against "arachnolysin," a toxine found in spiders. In this case the complete immunity of the red blood cells of the guinea pig against arachnolysin is accounted for by the entire absence of the proper receptors, while the susceptibility of the red blood cells of the rabbit to very small quantities of this poison is accounted for by the strong combining affinity which exists between these cells of the rabbit and the arachnolysin.

In some cases the production of receptors may apparently be traced in the development of certain species. Cannus and Gley<sup>b</sup> have followed the development (?) of the receptors in the red blood cells of the rabbit toward the hemolysin found in eel serum. Young rabbits are much less susceptible to this poison than adult rabbits, which is accounted for by Ehrlich as being due to a gradual development of the receptors having proper combining affinities for the hemolysin found in the eel serum.

The union between the receptor of the cell and its poison is not always a direct one, as described above, but sometimes takes place

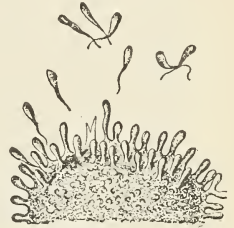


FIG. 1f.—Fourth stage; the receptors have left the cell and float free in the blood = anti-toxin.



FIG. 1g.—The neutralization of a toxin by antitoxin; the free receptors in the blood have united with the toxin = anti-toxic immunity.

<sup>a</sup>Sachs, Hans: Hofmeisters Beitr., bd. 2, h. 1-3.

<sup>b</sup>Quoted by Ehrlich, loc. cit.

through the intervention of a second body, known variously as the amboceptor, *zwischenkörper*, immune body, sensitizer, fixative, preparative, *desmon*, etc.

This order of immunity is particularly evident in the poisons that have a lytic or dissolving action upon bacteria or the cells of the body, such as the bacteriolytins, hemolytins, and other cytolytins. These poisonous bodies are believed by Buchner to be a ferment, and are usually spoken of as the "complement," but also as the "alexin" (Buchner) or "cytase" (Metchnikoff).

One of the remarkable facts connected with the phenomena of the lytic poisons is that the poison itself, usually called the complement, is normally present in the blood. The complement has less resistance to heat than the intermediary body, and is therefore spoken of as being thermolabile.

According to Ehrlich's theory, immunity can only be obtained against the intermediary body, which is believed to be specific. This intermediary body has a greater resistance to heat than the complement; that is, it is relatively thermostabile.

Ehrlich compares the intermediary body with diazo-benzaldehyde, which by means of its diazo group is capable of combining with a series of bodies, such as aromatic amines, phenols, keto-methyl bodies, etc., while by means of its aldehyde group it may combine with a different series, such as the hydrazins, ammonia radicals, and hydrocyanic acid. Phenol and hydrocyanic acid will not directly combine, but with diazo-benzaldehyde acting as an intermediary body, these two substances can be brought into combination. Pushing this comparison further, we may say that the aromatic body, or the phenol, represents a constituent of the blood corpuscle. The diazo-benzaldehyde is the intermediary body, while the poisonous hydrocyanic acid constitutes the complement.<sup>a</sup>

Welch<sup>b</sup> very ingeniously extended Ehrlich's conception of immunity to the bacterial cell. According to Welch's views the bacterial cell has the same power of defensive action against the poisons produced by the cells of higher animals that they have against the toxic products of the bacteria.

<sup>a</sup> Vaughan and Novy: Cellular toxins, 1902, p. 131.

<sup>b</sup> Welch, William H.: The Huxley lecture on recent studies of immunity with special reference to their bearing on pathology. Bull. Johns Hopkins Hosp., Balto., v. 13, (141), Dec., 1902, pp. 285-299.



FIG. 1h.—The second order of immunity, showing the complement and immune body.

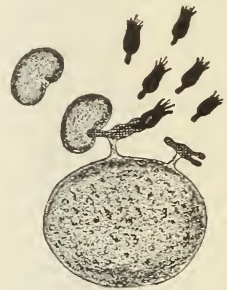


FIG. 1i.—The third order of immunity, showing an immune body having two affinities.

In other words, there is a chemical battle. Both the bacterial cell and the body cell excrete poisonous substances against each other, and both in turn are building up a chemical defense against the action of these respective poisons.

## THE IMMUNITY UNIT.

The unit for measuring the strength of diphtheria antitoxin established by Ehrlich is a measure of strength, not of quantity.

It is difficult to define the unit in a brief sentence. A proper understanding of it may only be had from a study of the theoretical considerations involved.

The unit may be defined as the neutralizing power possessed by an arbitrary quantity of diphtheria antitoxic serum kept under special conditions to prevent deterioration in an authorized laboratory.

From a theoretical view point the unit may be defined as that quantity of diphtheria antitoxic serum which will just neutralize 200 minimal lethal doses of a pure poison. By a "pure" poison is understood one containing only *toxin*, and no *toxoid*, *toxone*, or other substances capable of uniting with the antibodies.

The test by which the strength of antitoxin contained in a unit is measured is a physiological one and depends upon the neutralization of the toxine by the antitoxin. This neutralization can only be determined by injecting the toxine and antitoxin mixtures into guinea pigs, which animals are highly susceptible to the diphtheria bacillus and its poisons.

In order to obtain a fundamental understanding of Ehrlich's immunity unit it is necessary to make a study of the nature of the various poisonous substances which are present in the diphtheria toxine, and then clearly to understand the combining and neutralizing action which these poisons exert upon the antitoxin. Both of these subjects are treated more fully in the next chapter.

In all the earlier work on this subject the toxine was used as a basis for measuring the strength of the antitoxin, but as the toxine is a much more complex substance than the antitoxin, and as it is less stable, accurate results were not possible. Ehrlich showed that the antitoxin under certain conditions was permanent, both in power of chemically combining with and physiologically neutralizing the toxine.

The unit for measuring the strength of diphtheria antitoxin is an arbitrary quantity, just as the units of all systems of weights and measures are fundamentally arbitrary quantities, so that the question of the quantity of immunity units which a particular diphtheria antitoxic serum contains can only be determined by comparing it with the



standard serum preserved by Ehrlich in the Klg. Institut für Experimentelle Therapie at Frankfort a. M., Germany. This serum has been carefully tested, its antitoxic strength is accurately known, and by comparing any other serum with this original one its antitoxic value may be determined.

Ehrlich, however, does not admit that his antitoxic unit is such an arbitrary quantity, and believes that he can reproduce it should it become lost, by a study of the peculiar relations which exist between the combining and neutralizing power of toxins and antitoxins; for, from a theoretical point of view, Ehrlich<sup>a</sup> considers that the immunity unit contains just 200 "combining units." A combining unit is analogous to the valence in chemistry, and Ehrlich has shown by his study of various diphtheria poisons that the antibodies in his immunity unit have 200 of these combining affinities. As each combining affinity represents one minimal lethal dose, the immunity unit theoretically should combine with and neutralize 200 MLD's of a toxine containing only *toxin*. If it were possible to obtain the *toxin* in pure solution, free from *toxoids*, *toxones*, and other substances which have the power of uniting with the antibodies, it would then be comparatively easy to demonstrate the number of minimal lethal doses which the immunity unit is able to neutralize. As such pure poisons are practically never obtained, the immunity unit in actual practice is found to neutralize many times less than 200 minimal lethal doses of the toxine (from 16 to 136), the remaining combining affinities being satisfied by such allied substances as *toxoid*, *toxone*, etc., which have the same chemical affinity for the antitoxin, but diminished poisonous properties.

In order the better to understand Ehrlich's immunity unit it will be necessary to give a brief review of its development. In all the earlier systems of measuring the potency of diphtheria antitoxic serum the diphtheria culture or its toxine was the basis of measurement. Behring and Roux both first used living cultures. Behring substituted the use of the soluble diphtheria poison for living cultures as early as 1893, as he found it was impossible to establish any system of definite dosage with live organisms.

The method at first used by Roux for determining the strength of antitoxic serum was based upon the ratio between the quantity of the serum necessary to protect a guinea pig and the weight of that guinea pig. His method was carried out as follows: A certain quantity of

<sup>a</sup> Ehrlich: Die werthbemessung des diphtherieheilserums und deren theoretische grundlagen. Klin. jahrb., Jena, v. 6 (2), 1897, pp. 299-326.

Ehrlich: Ueber die constitution des diphtheriegiftes. Deut. med. woch., Leipzig, v. 24 (38), Sept. 22, 1898, pp. 597-600.

Ehrlich: Ueber die giftcomponenten des diphtherietoxins. Berl. klin. woch., 1903, nos. 35-37, p. 37.

diphtheria antitoxic serum, say 0.01 c. c., was injected subcutaneously into a guinea pig. Twelve hours later, 0.5 c. c. of a fresh virulent culture of the diphtheria bacillus was inoculated into the guinea pig, weighing, say, 300 grams. If the guinea pig lived, 0.01 c. c. of the serum was considered sufficiently active to protect 300 grams of guinea pig, and 1 c. c. of the serum would consequently protect 30,000 grams of guinea pig, and the strength of the serum was expressed as 1:30,000. The strength of a serum according to this method was expressed in such figures as 1:100,000 or 1:500,000.

Control animals were inoculated to insure the virulence of the culture used. The culture used was considered sufficiently virulent if the control guinea pig died within thirty hours.

A serum with an immunizing strength of 1:100,000 meant that 1 c. c. would protect 100,000 grams of guinea pig; and a serum whose strength was 1:500,000 meant that 1 c. c. of the serum would protect 500,000 grams of guinea pig against a certainly lethal dose of diphtheria culture or later the toxine when injected in accordance with the above procedure.

Madsen<sup>a</sup> showed as a result of comparative tests that the German method of expressing the strength of antitoxic sera in antitoxin units was quicker, cheaper, easier, and more accurate than the French method devised by Roux. He showed that with the French method it is often impossible to determine differences as great as 1:100,000 and 1:200,000. This method was finally abandoned by Roux himself in favor of the German procedure.

In the earlier methods of testing the strength of diphtheria antitoxin, according to both the methods of Behring and Roux, the two substances were always inoculated separately into a guinea pig, usually in different places. Sometimes the toxine and antitoxin were inoculated at different times in order to make a distinction between the immunizing power of a serum and its curative power.

The method devised by Ehrlich in collaboration with Kossel and Wassermann in 1894<sup>b</sup> was based upon an entirely new principle. The scientific researches of Behring and Kitasato had previously established the fact that tetanus poison and its antitoxin neutralize each other in a test tube outside of the body. Ehrlich, Kossel, and Wassermann satisfied themselves that this neutralization between the diphtheria poison and its antibody takes place at once when the two substances are mixed in a test tube, and they believed at that time (1894) that it took place in accordance with the law of simple proportions.

<sup>a</sup>Madsen, Thorvald: Ueber messung der stärke des antidiphtherischen serums. Zeitschr. f. hyg., Leipzig, v. 24, pp. 425-442.

<sup>b</sup>Ueber Gewinnung und Verwendung des Diphtherieheilsersums. Deut. med. Woch., 1894, no. 16.

In the methods used before this time (1894), when the toxine and antitoxin were injected separately into the guinea pig the substances first met each other in the body of the animal. The time it takes for the toxine to meet and neutralize the antitoxin when these substances are injected separately into an animal naturally varies with the individual conditions of absorption, and exact results therefore were not possible. It was found, on the other hand, that if the two substances are mixed in a test tube and the mixture is injected into guinea pigs, constant and uniform results are obtained.

At this time (1894) an old test toxine, obtained by Behring and preserved with 0.5 per cent phenol, was used as a basis for measuring the strength of the antitoxic serums. Ten times the minimal fatal dose of this toxine for a guinea pig weighing 200 to 300 grams was mixed with varying quantities of serum the strength of which was to be determined. The mixture was at once inoculated into guinea pigs and the animals closely watched for local reaction at the site of inoculation, for loss of weight or other symptoms. As the symptoms appear in a few days it was possible, in carrying out the tests according to this method, to determine the strength of an antitoxin in a short time.

This is Behring's method of measuring the strength of diphtheria antitoxic serum.

The strength of the serum was determined in accordance with the tests carried out by Behring's method, as that quantity of serum which completely neutralized the ten minimal fatal doses. The toxine was considered to be completely neutralized if the guinea pig showed neither local nor constitutional effects of any kind. At that time (1894) Ehrlich considered the method as outlined above to be trustworthy, and established an ANTITOXIN UNIT as that quantity of serum which required just 1 c. c. to neutralize ten times the minimal fatal dose of the diphtheria poison. The antitoxic serum, which had precisely this power, he considered as a normal serum.

Later von Behring and Ehrlich found stronger serums and modified the unit, which they now call the immunity unit, to be that quantity of antitoxin, viz, antidiphtheritic serum, which will neutralize  $100 \times$  MLD for a guinea pig weighing 250 grams. Ehrlich's method for carrying out the tests in accordance with this new conception was as follows:

Ten times the minimal fatal dose is mixed with a definite quantity of serum and this mixture injected subcutaneously into a guinea pig. If the guinea pig lives the quantity of the serum used contains at least one-tenth of an immunity unit.

For example, if the minimal fatal dose of toxine is 0.005, ten times this quantity, or 0.05, represents ten times the minimal lethal dose ( $10 \times$  MLD).

The proper quantity of the toxine and an amount of the antitoxin to be tested are now mixed in a test tube, as follows: To 0.05 c. c. of the toxine is added 0.001 c. c. of the serum, and the mixture inoculated subcutaneously into a guinea pig. If there was sufficient antitoxin in the 0.001 c. c. of the serum used to neutralize the 10 MLD's used, the pig would survive, and it was then considered that 0.001 c. c. of that serum contained at least one-tenth of an immunity unit, and that 1 c. c. of that serum would consequently contain at least 100 units.

Attention is particularly called to the fact that at first the strength of antitoxin depended upon the complete neutralization of the poison as determined by indications of sickness in the guinea pig, particularly changes at the site of inoculation. Slight swellings which disappear in a few days were not taken into consideration in determining the value of the serum. It is evident that the indications of sickness in the guinea pig or the presence of slight changes at the site of inoculation are dependent upon subjective considerations leading to differences of opinion or errors in judgment which could materially affect the accuracy of the tests.

A partial neutralization of the poison sufficient to save the life of the animal is a more definite factor than the complete neutralization depending upon the appearance of local signs for recognition.

On account of these difficulties encountered in determining the value of antitoxins it became necessary to eliminate all subjective considerations and obtain a method based upon strictly objective conditions. Both Ehrlich and von Behring independently came to the conclusion that the *death* of the animal was a much better criterion for determining the value of a serum than the local reactions or the survival of the animal heretofore depended upon.

A still more radical change in the principle of measuring the strength of diphtheria antitoxin was now introduced.

Up to this point the basis of measuring the strength of diphtheria antitoxin was always either the culture of the diphtheria bacillus or its poisonous products. The genius of Ehrlich disclosed errors in the methods heretofore described. His researches into the biological relations between toxine and antitoxin showed that it required varying amounts of antitoxin in order to neutralize the 10 MLD's. He finally showed that there is no relation between the poisonous effects of the toxine and its power of combining chemically to neutralize the antitoxin. He showed that a toxine may be weakened very materially by the influence of time, light, heat, oxygen, and other deleterious influences, without, however, altering its power of combining with antitoxin. This discovery was of fundamental importance and required the transfer of the standard of measurement from the poison to its antibody.



Ehrlich<sup>a</sup> now made numerous researches in order to determine the stability of the antitoxin. He had particular success with a serum containing a high percentage of glycerin. This glycerinated serum showed exactly the same power of neutralizing toxine after one year that it did at first.

For a while this glycerin solution of antitoxic serum was used as the basis for standardizing serums. But Ehrlich showed that even glycerinated serum may weaken and also the fact that because the neutralization point does not vary is no guaranty of the stability of the test solution. It was therefore necessary to abandon the glycerinated serum as a method for preserving the standard unit. The principal factors which cause the weakening of antitoxin are moisture, oxygen, light, and heat.

It is very easy to guard against the deleterious influences of light and heat. It was therefore necessary only to pay particular attention to the first two agents.

The serum was therefore reduced to a powder under proper precautions and this dried blood serum preserved in a small glass apparatus consisting of two parts connected by means of a glass tube. The serum is placed in one portion of the apparatus and phosphoric anhydrid, which is a very powerful dehydrating substance, in the other. The air is exhausted as much as possible by means of a high vacuum and the apparatus hermetically sealed. After a few days the acid will have taken up all the moisture from the serum, and the tube connecting the two parts may then be melted and sealed off, separating the acid from the serum. The dried serum is now contained in a vacuum tube and preserved in a cool place in absolute darkness.

In this way Ehrlich prepared a great number of these little tubes, each one containing a dried serum whose value was accurately determined. Each tube contained 2 grams of the dried serum, representing 1,700 immunity units in each gram. Every two or three months one of these tubes is carefully opened and the contents dissolved in 200 c. c. of a 10 per cent solution of sodium chlorid and glycerin mixture, the mixture containing from 50 to 80 per cent of glycerin. One c. c. of this glycerinated serum represents then exactly seventeen times the normal strength; and therefore if we dilute 1 c. c. of this glycerinated serum with 16 parts of water, each cubic centimeter of the dilution contains one immunity unit.

Although the serum is used as a basis for standardizing the strengths of other sera, the toxine still plays a very important rôle in the process of testing, as it is manifestly impossible to estimate the strength of an

<sup>a</sup> Ehrlich: Die Wertbemessung des Diphtherieheilsperms und deren theoretische Grundlagen. Klin. Jahrb., Jena, v. 6 (2), 1897, pp. 299-326.

antitoxic serum by comparing it directly with another serum. One is compared with the other through the toxine.

It is not the absolute toxicity of the poison which is considered in testing the strength of the antitoxin, but a combination of its combining and poisonous powers, as expressed in the L+ dose (see p. 26). The method by which the strength of standard serum is estimated and methods by which other serums are compared with it are fully considered in detail in the following pages.

It is to be noted here that in accordance with the method of determining the power of diphtheria antitoxin, as devised by Ehrlich, three important factors are achieved: The poison is neutralized, and the protective and curative powers of the serum established.

## THE CONSTITUTION OF THE TOXINE AND ITS RELATION TO ANTITOXIN.

Ehrlich's discovery that the relation between toxine and antitoxin is not always the same led him to investigate the constitution of the diphtheria poison.

It is believed that the diphtheria bacillus primarily secretes at least two poisons, the *toxin* and the *toxone*.

The *toxin* is not stable and is readily reduced to *toxoid*. For the purposes of our work we must have a clear understanding of the *toxin*, the *toxoid*, and the *toxone*.

The *toxin* is the only poison produced by the diphtheria bacillus capable of causing acute death. The *toxoids* have little or no poisonous properties. The *toxones* produce the late manifestations of paralysis.

The interesting point about all of these poisons is, they have the power of combining chemically with the antitoxin. In other words, *toxin*, *toxoid*, and *toxone*, and finally *epitoxonoid*, all have the same haptophore group, but different or modified toxophores.

The poisonous *toxins* are subdivided into three groups depending upon the degree of their avidity for antitoxin, viz, *prototoxin*, *deutrotoxin*, and *tritotoxin*. Each of these *toxin* groups may in whole or in part be converted into *toxoids*, which are not poisonous but which have the same power of combining with the antitoxin as the *toxin* from which they derive their origin. These altered *toxins* are consequently known as *prototoxoid*, *deutrotoxoid*, and *tritotoxoid*, respectively. The *prototoxin* has a greater affinity for antitoxin than the *deutrotoxin*, and the *deutrotoxin* has a greater affinity for antitoxin than the *tritotoxin*. The same relation holds good for the three *toxoids*.

As each diphtheria poison contains these substances in varying proportions it is at once evident that there can be no relation between the toxicity of the poison and its combining power with antitoxin. Take for example two poisons which require the same dose to kill, but in one the *prototoxin* and in the other the *tritotoxin* has become altered into *prototoxoid* and *tritotoxoid*, respectively. It is then evident that in order to neutralize the same lethal dose in the first case it would require more serum than in the second, because in the first case a certain proportion of the antitoxin would be used up by combining with the *prototoxoid*, which is nonpoisonous, leaving a proportionately greater amount of uncombined *toxin*. On the other hand, a serum tested against ten or one hundred minimal lethal doses of these respective poisons would appear to have quite different immunizing values.

The *toxone* is one of the primary metabolic products of the diphtheria bacillus. It possesses the same haptophore group as the *toxin*, but has far less avidity for antitoxin. When the diphtheria poison and antitoxin are brought together the *toxone* is the last to enter into combination with the antitoxin, as both the *toxin* and *toxoid* have greater affinities for the antibodies than the *toxone*. The *toxone*, as before mentioned, has the same haptophore group as the *toxin* but has a different toxophore group, as it is incapable of producing acute effects, cutaneous necroses and death, but is responsible for the local edema and the diphtheritic paralysis.

The diphtheria poison is first investigated biologically by adding varying quantities of the poison to the immunity unit and inoculating the mixtures into a series of guinea pigs. In this way it is very evident, as Ehrlich has shown, that two limits, boundaries, or zones are always shown, which are of the greatest importance in determining the nature and composition of the poison. Each of these limits is designated by the letter L, from *limes*, a boundary or zone.

These limits are known, respectively, as  $L^0$  ( $^0$ =nil) and  $L+$  ( $+$  = death).

By  $L^0$  is meant that quantity of poison which just neutralizes or saturates one immunity unit as shown at the necropsy done forty-eight hours after the subcutaneous injection of the mixture into the guinea pig. The reaction at the site of the inoculation at this examination must be hardly noticeable.

Theoretically the  $L^0$  dose of toxin must unite with and neutralize just 200 "combining units" of antitoxin. The  $L^0$  dose, therefore, contains just 200 minimal lethal doses of a theoretically pure poison.

By  $L+$  is meant the smallest quantity of toxin that will neutralize one immunity unit, plus a quantity necessary to kill the animal on the fourth day. As defined by Ehrlich, the  $L+$  dose is that quantity of poison which, despite the antibodies contained in one immunity unit of serum, contains a sufficient excess of the poison to cause the death of the guinea pig within the course of four days.

In studying the constitution of the diphtheria poison it is also necessary to determine its absolute toxicity with the greatest possible precision. The absolute toxicity of the diphtheria poison is usually spoken of as the minimal lethal dose (MLD), sometimes as the minimal fatal dose (MFD), and occasionally as the simple lethal dose. The determination of the minimal lethal dose is often an exceedingly tedious problem, and in some cases requires as many as 100 animals. This is due in part to the fact that the determination of the exact limits is largely influenced by the individuality of the guinea pigs, so that it is necessary to repeat the work on a series of animals in order to reach an average.



The minimal lethal dose may be defined as that quantity of toxine which will surely kill every guinea pig weighing 250 grams in the course of four days or, at the very latest, five days. As Ehrlich has pointed out, such a quantity may kill some of the animals sooner, that is, within thirty-six to forty-eight hours. A quantity of diphtheria poison that will kill every guinea pig, without exception, acutely, within thirty-six to forty-eight hours, contains more than the minimal lethal dose.

The L+ dose is a much more definite and constant factor than the MLD. It does not show the irregularities or present the difficulties met with in determining the absolute toxicity of the poison.

In his earlier work Ehrlich looked upon the diphtheria toxine and antitoxin as simple substances neutralizing each other as an alkali does an acid. That the relation between these two substances is much more complex was at once evident as soon as he worked out the complex nature of the diphtheria poison.

The best method of studying the relations between toxine and antitoxin is by mixing these two substances together in varying amounts and studying the effects of partial saturation or neutralization. As the immunity unit is supposed to contain 200 "combining units," the most valuable information is obtained by adding one two-hundredths of the immunity unit to a given quantity of toxine, using either the L<sup>0</sup> or L+ dose of toxine. These mixtures, inoculated into a series of guinea pigs of standard weight and under standard conditions, will give certain definite results.

By mixing with the L<sup>0</sup> dose of the diphtheria toxine such fractional amounts of antitoxin we have results which may be summarized as follows:

At first these mixtures may show no diminution in toxicity, despite the addition of considerable (say, forty two-hundredths) of the immunity unit. This zone represents the *prototoxoids*. Then comes a time when for each addition of one two-hundredth of a unit of antitoxin the poison may lose one minimal lethal dose. This is the zone of *toxins* (*syn-toxins*). Then follows the zone in which the mixture fails to produce acute death, but may cause local edema and later paralysis. This is the zone of *toxones*, first called *epitoxones* by Ehrlich.

Later, von Dungern<sup>a</sup> showed the presence of *epitoxonoids* which have the same combining affinity for the antitoxin, but show no poisonous properties. The *epitoxonoids* of von Dungern explain the power of neutral mixtures of toxine and antitoxin to produce immunity when injected into susceptible animals.

The results of the partial saturation or neutralization tests are conveniently studied by plotting curves, called by Ehrlich "spectra." Several such spectra are shown in fig. 2.

<sup>a</sup>Beitrag zur Kenntniss der Bindungsverhältnisse bei der Vereinigung von Diphtheriegift und Antiserum. Deut. med. woch., v. 30 (8-9), 1904, pp. 275-277, 310-312.

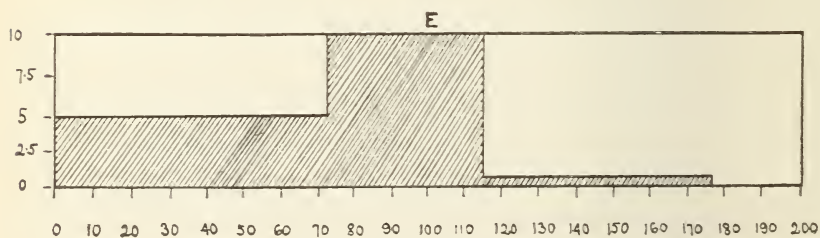
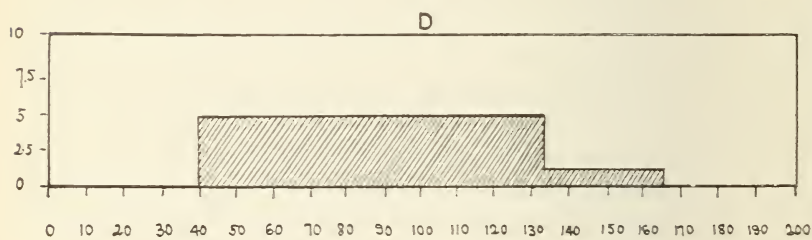
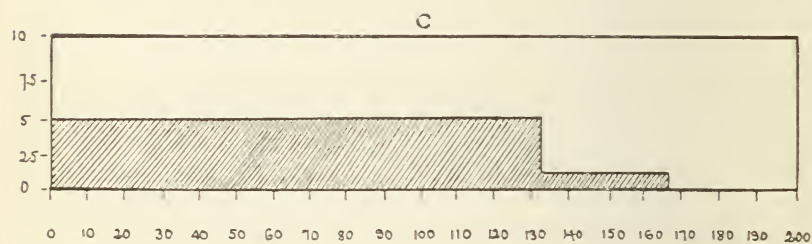
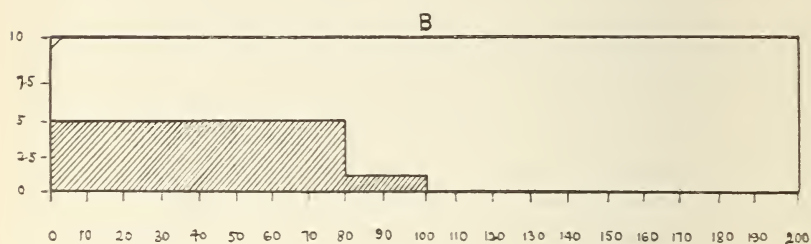
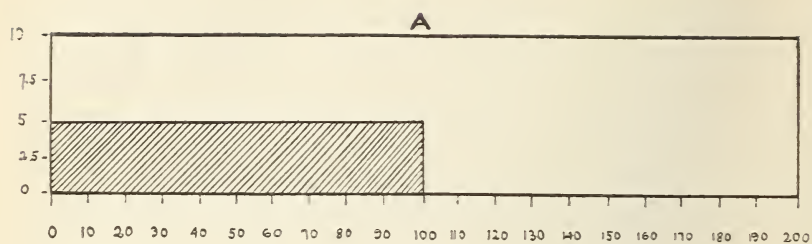


FIG. 2 — Ehrlich's spectra.

In studying these spectra, it must be remembered that one immunity unit theoretically neutralizes 200 minimal lethal doses of a pure poison, containing only *toxin*. It is self-evident that such *toxin* "valences" may be substituted by other substances having the same combining affinity but less poisonous or not at all poisonous, such as *toxoid* and *toxone*.

As toxines containing only *toxin* are practically never obtained, it is evident that the immunity unit will be found in actual practice to neutralize a less number of minimal lethal doses than 200, the remaining number being satisfied with the *toxoids* and *toxones*.

In order to obtain a correct understanding of these spectra, it is necessary to know how one is cast. The most instructive results are obtained by using the  $L^0$  dose of toxine. The  $L^0$  dose is that quantity of toxine which will just neutralize one immunity unit. The  $L^0$  dose should contain just 200 MLD's of a theoretically pure toxine, containing only *toxin*.

Let us make a spectrum of an impure toxine containing the following:

$$\begin{array}{r} L^0 = 50 \text{ combining units of } \textit{prototoxin}. \\ 100 \text{ combining units of } \textit{toxin} (=100 \text{ MLD's}). \\ 50 \text{ combining units of } \textit{toxone}. \\ \hline 200 \end{array}$$

Then:

$L^0$  dose of toxine = 100 MLD's, i. e., contains enough *toxin* to kill 100 guinea pigs.

$L^0 + \frac{1}{200}$  immunity unit = 100 MLD's.

$L^0 + \frac{49}{200}$  immunity unit = 100 MLD's.

$L^0 + \frac{50}{200}$  immunity unit = 100 MLD's.

Up to this point we see that the addition of fifty two-hundredths of the immunity unit has no effect upon the toxicity (*toxin*) of the poison. In other words, the antitoxin is being used up by combining with some nonpoisonous substance, viz, *prototoxoid*. The first 50 segments of our spectra will therefore consist of this modified *toxin*.

If now we add more antitoxin to our toxine we will find that for the addition of each one two-hundredths of the immunity unit the toxine loses one MLD—

$L^0 + \frac{51}{200}$  immunity unit = 99 MLD's.

$L^0 + \frac{70}{200}$  immunity unit = 80 MLD's.

$L^0 + \frac{1}{2} \frac{99}{200}$  immunity unit = 3 MLD's.

$L^0 + \frac{1}{2} \frac{98}{200}$  immunity unit = 2 MLD's.

$L^0 + \frac{1}{2} \frac{99}{200}$  immunity unit = 1 MLD.

That is, the  $L^0$  dose of toxine plus one hundred and forty-nine two-hundredths of the immunity unit contains in the mixture just enough

free poison (*toxin*) to kill one guinea pig. Therefore the next 100 segments of this spectrum will consist of *toxin*.

If we now add one two-hundredths more of antitoxin the mixture will fail to kill. Thus,

$L^0 + \frac{15.0}{200}$  immunity unit = will not kill acutely, but causes paralysis (*toxones*).

$L^0 + \frac{19.7}{200}$  immunity unit = will not kill acutely, but causes paralysis (*toxones*).

$L^0 + \frac{19.8}{200}$  immunity unit = will not kill acutely, but causes paralysis (*toxones*).

$L^0 + \frac{20.0}{200}$  immunity unit = complete neutralization.

The last 50 segments of the spectrum would, therefore, be made up of *toxone*.

The spectrum of this poison would, therefore, be expressed as follows:

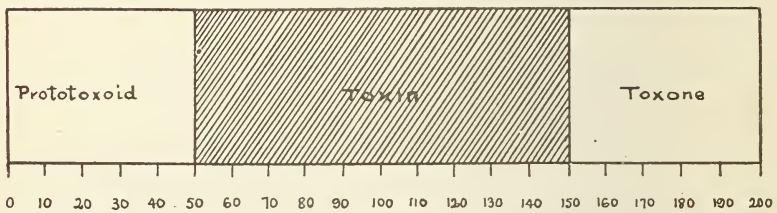


FIG. 3.—A spectrum of a simple poison. Redrawn from Madsen, *La Constitution du poison diphthérique*. *Ann. de l'Institut Pasteur*. Vol. XIII, 1899, p. 576.

By this graphic representation of the results of the studies of toxine-antitoxin mixtures it is possible to tell at a glance the proportional amounts of *toxin*, *toxoid*, or *toxone* contained in a given poison.

The following instructive instance is taken from Ehrlich's poison No. 5:<sup>a</sup>

$L^0$  dose of this toxine No. 5 was 0.125 cc.

$L+$  dose of this toxine No. 5 was 0.25 cc.

MLD dose of this toxine No. 5 was 0.0025 cc.

It will, therefore, be seen that the  $L^0$  dose of this particular toxine contained exactly  $50 \times$  MLD, and the  $L+$  dose contained  $100 \times$  MLD.

The gradual changes which this poison underwent, as shown by the spectra, may be explained as follows:

In A (fig. 2) pure *hemitoxin* is shown. By this is meant that the addition of each one two-hundredths of the immunity unit to the  $L^0$

<sup>a</sup> Ehrlich: Ueber die constitution des diphtheriegiftes. *Deut. med. woch.*, Leipzig, v. 24 (38), 1898, pp. 597-600.

Ehrlich: Ueber die giftcomponenten des diphtherietoxins. *Berl. klin. woch.*, 1903, nos. 35-37.



dose takes away just one-half MLD until 100 such combining units, or one-half of the immunity unit, has been added. A further addition of antitoxin had no effect upon the *toxin* as shown by death or necroses, but only influenced the *toxone*.

In B (fig. 2), instead of an equal mixture of *toxin* and *toxoid*, known as *hemitoxin*, we have a mixture of *toxin* and *toxoid*, containing more of the latter than the former, as indicated by the diminished toxicity. The evidence of *tritotoxin* is shown in the spectra between 80 and 100.

Phase D (fig. 2) shows a further loss of toxicity of this poison No. 5 under consideration. By this time the minimal lethal dose had risen to 0.004. It will be seen that the addition of forty two-hundredths of the immunity unit had no influence upon the toxicity of the poison, indicating the appearance of *prototoxoid*.

Three distinct zones may be distinguished in such spectra.

The first zone, which is not always present, represents the non-poisonous *prototoxoid*.

The second zone contains the poisonous *toxin*.

If the addition of  $\frac{1}{20}$  of the immunity unit, which represents one combining unit, removes exactly 1 MLD, the poison then contains pure *toxin*. Sometimes the addition of one combining unit removes on the average one-half the lethal dose. This phenomenon is interpreted as indicating the mixture of equal parts of *toxins* and *toxoids*, designated by Ehrlich as *hemitoxin*. The existence of *hemitoxin* is possible only in case the *toxoid* has precisely the same avidity for the antitoxin as the *toxin*. From this it follows, as Ehrlich had from the beginning assumed and as Arrhenius has confirmed, that in the transformation of *toxin* into *toxoid* no change in avidity occurs.

Pure *toxoid* occurs often in the form of a *prototoxoid*, which possesses a stronger affinity for antitoxin than all other components of the poison. The *prototoxoid* manifests its presence by the fact that a certain quantity of antitoxin may be added to the diphtheria poison without in the slightest degree lessening its toxicity.

The third zone, which Ehrlich calls the "toxone zone," has been subject to the greatest amount of discussion and the correctness of his views has been questioned, especially by Arrhenius and Madsen.<sup>a</sup> Arrhenius insists that instead of considering the diphtheria poison to contain *toxin* and *toxone*, it would be simpler to consider it as a single (homogeneous) substance which has a very weak affinity for the antitoxin, and that in mixtures containing *toxine* and antitoxin there is always both free *toxine* and free antitoxin. He draws his analogy from known facts in physical chemistry, particularly from studies upon

<sup>a</sup>Toxines et antitoxines le poison diphtérique. Acad. roy. sci. et let. Danemark: Bull. no. 4, 1904. pp. 269-305.

the relation of boracic acid and ammonia. These two substances have a comparatively weak affinity for each other, and in mixtures all the boracic acid does not combine with the ammonia, but there is always present both free ammonia and free boracic acid.

When ammonia and boracic acid are brought together in watery solution some of the ammonia at once unites with some of the boracic acid and forms ammonium borate. This reaction starts with a certain velocity, but as the mass of ammonium borate increases, the velocity of the reaction gradually diminishes. After a time a condition is reached when the ammonium borate has a maximum value and does not further increase, no matter how long the reaction is allowed to proceed under the given conditions.

When this condition of equilibrium is reached the mass contains a constant quantity of water, ammonia, boracic acid, and ammonium borate; but these substances are not at rest. The ammonia and boracic acid will always react when in the presence of each other whether or not ammonium borate is present. But as the proportionate amount of ammonium borate remains constant, it is understood that while this continuous association between the ammonia and the boracic acid is going on there is, at the same time, a reversible action—that is, a dissociation of the ammonium borate to re-form ammonia and boracic acid. These two reactions take place simultaneously.

Arrhenius believes that the diphtheria poison changes slowly, according to the laws of monomolecular reactions, into a nonpoisonous body—toxoid. Both substances, toxin and toxoid, according to Arrhenius, combine feebly with antitoxin, the equilibrium constant being equal for both.

Ehrlich, however, contends on the other hand that the diphtheria poison is not only a complex substance, but that the *toxin* and antitoxin have strong affinities for each other. He admits that the long interval between the values of  $L^0$  and  $L+$  seems to oppose the acceptance of a strong affinity between the *toxin* and antitoxin.

Designate by  $D$  the amount of toxine representing the difference between  $L+$  and  $L^0$ . From chemical examples it can be easily shown that with poisons of strong avidity the value of  $D$  must correspond exactly to one minimal lethal dose, whereas with poisons of weak affinity  $D$  may be much larger on account of the free or dissociated poison. Ehrlich, however, finally succeeded in finding a toxine in which  $D$  was precisely of the theoretic value of 1. Thereby it was in principle shown that *toxin* and antitoxin unite with strong affinity, and the great variation, from 0 to 300 per cent, in the value of  $D$  represented by different specimens of toxines could be explained by the presence of *toxone*.

In his recent very careful work upon the constitution of diphtheria poison and the relation between toxine and antitoxin, von Dungern<sup>a</sup> concludes that—

1. The union of diphtheria toxine and antitoxin does not proceed in accordance with the ammonia-boric acid scheme.

2. The observed phenomena of combination are explicable only upon the assumption of a complex constitution of the diphtheria poison.

3. The facts find their best explanation in the action of a *toxone* and an *epitoxonoid*. *Epitoxonoid* is present in considerable quantity in toxic broth. The immunizing action of apparently completely neutralized toxins can therefore be explained.

4. Constituents of the diphtheria poison with weak affinity after combining with antitoxin may eventually become so firmly bound that this union can only be incompletely broken by toxin of stronger avidity. The strength of the combination is of significance for the action of antitoxin.

The claim of Arrhenius and Madsen that the toxine is a simple substance having a weak affinity for the antitoxin, and that the combination of toxine and antitoxin follows the Guldberg-Waage law, and that the reaction is therefore reversible, seems, in the light of the evidence before us, to be untenable.

Nernst<sup>b</sup> and Michaelis<sup>c</sup> consider that the assumption that the reaction is reversible, at least after a very short period, is arbitrary and unsupported by evidence. In addition to von Dungern,<sup>a</sup> as above quoted, Sachs,<sup>d</sup> Morgenroth,<sup>e</sup> and others have brought forward new experiments to show that the reaction is not reversible, and that the existence of *toxoids* and *toxones* is very probable.

The question as to the existence of *toxones* now seems by the work of Calcar, if confirmed, to be definitely settled in favor of Ehrlich's views. Calcar<sup>f</sup> separated from diphtheria bouillon by special methods of filtration, through a membrane, two poisonous constituents. The one (Ehrlich's *toxin*) killed acutely; the other (Ehrlich's *toxone*) produced late paralysis and death after several weeks.

Ehrlich and his co-workers had been able to show the existence of *toxones* only by more indirect methods (partial neutralization of toxine

<sup>a</sup> Deut. med. Woch., 1904, Nos. 8 and 9.

<sup>b</sup> Zeit. f. Elektrochem., 10, p. 377.

<sup>c</sup> Biochem. Centrbl., 3, p. 1.

<sup>d</sup> Berl. klin. Woch., 41, p. 412.

<sup>e</sup> Ibid., 41, p. 526.

<sup>f</sup> Ibid., 41, p. 1028.

with antitoxin), and lack of direct proof of their existence gave Arrhenius and Madsen's contention that the *toxones* were only the *toxin* which was being slowly freed from the antitoxin-toxine combination a certain degree of plausibility.<sup>a</sup>

Calcar was also able to show that the *toxones* have a greater molecular volume than the *toxins*, but a smaller molecular volume than the proteids.

It therefore seems plain, as Ehrlich states, that his views furnish a far better explanation than those of Arrhenius of numerous facts in the domain of toxins, such as the process of spontaneous enfeeblement of *toxins*, their passage into a state of stability, the reduction of the *toxone* zone, and the capacity of completely neutralized poisons to produce antitoxin (Park) by means of von Dungern's *epitoxonoids*.

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<sup>a</sup> Reid Hunt in Gould's Amer. Yearbook of Med. and Surg., 1905, p. 649.



## THE TOXINE.

### PREPARATION OF THE TOXINE.

*The culture.*—For the preparation of the toxine we use a culture known as “Park’s bacillus No. 8.” This culture has now become famous in laboratories both in this country and abroad on account of its remarkable power of retaining its virulence and producing strong poisons. The culture was isolated in 1894 by Dr. Anna W. Williams, of the New York health department, and is sometimes known as the Park-Williams bacillus.

The best results are obtained by growing the organism as a surface growth in the special bouillon presently to be described. We carry it over from test tube to test tube every day, taking only the surface film with a flattened platinum needle.

The strongest poisons are obtained when the surface growth is heavy and the bouillon remains clear. A precipitate of the old and dead organisms always collects at the bottom of the tube.

*The bouillon.*—The bouillon is a special alkaline medium prepared from fresh lean beef freed of muscle sugar and all other sugars, and to which a small quantity of dextrose (glucose) is added, which seems to favor the production of a strong poison.

The bouillon is prepared largely in accordance with the instructions laid down by Theobald Smith in a paper entitled “The relations of dextrose to the production of toxin in bouillon cultures of the diphtheria bacillus.”<sup>a</sup> This culture medium, which we call “Smith’s bouillon,” is prepared by us as follows:

Cut out all the fat and tendon of the beef. Pass through the meat grinder, catching all the expressed juice. Weigh and add twice the weight of water. Place in the cool room at 15° C. for twenty-four hours, then strain through cloth, pressing firmly. Weigh the amount of meat infusion thus obtained. Take the reaction and neutralize with sodium hydrate to 1.5 per cent acidity to phenol-phthalin in order that the colon bacillus, which is now planted in it, may grow well. Inoculate with a reliable culture of *B. coli communis*, using 10 c. c. of a twenty-four-hour-old bouillon culture for each liter of meat infusion. Grow at 37° C. for twenty-four hours. Add the white of

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<sup>a</sup>Journ. Exper. Med., vol. 4, nos. 3-4, 1899.

one egg for each liter of infusion. Heat gently for twenty minutes to coagulate the albumin, and then filter while hot through paper. Weigh the amount of filtrate obtained and add sufficient water to make up the loss to the original amount. Take the reaction again and neutralize with sodium hydrate to an acidity of 0.5 per cent, then add 1 per cent peptone and one-half per cent sodium chlorid and 0.1 per cent dextrose. Heat again for twenty minutes in streaming steam in an open autoclav. Again take reaction, neutralize and repeat until the reaction of the infusion is just 0.5 per cent. The medium is now filtered through paper and filled into Fernbach flasks, test tubes, etc. These are sterilized in the autoclav at a temperature of 120° C. for twenty minutes.

The fermentation tubes prepared and sterilized without the addition of the 0.1 per cent of dextrose are now planted with a young culture of the colon bacillus and incubated forty-eight hours. If there is no muscle sugar present the growth stops sharply at the closed end without gas production and the reaction of the medium in the closed and open arms is about the same.

Test tubes are also filled and the final reaction is taken from the medium in one of the test tubes which were sterilized. The reaction is always found to rise about 0.1, due perhaps to the formation of acid salts by the heat of sterilization.

Our strongest toxines were obtained by adding the dextrose after the final sterilization and at the time of inoculation, confirming the results obtained by Hitchens working with Kinyoun.

The reaction of the bouillon used to grow the diphtheria culture is very important if we desire to obtain a strong poison. The reaction of the bouillon we use, 0.5 per cent acid to phenol-phthalin, is distinctly alkaline to litmus.

The diphtheria bacillus during the first period of its growth always produces an increased acidity in the bouillon. The culture used in this laboratory causes a marked rise in acidity during the first twenty-four or forty-eight hours and then a gradual change to alkali production, so that by the seventh day the reaction of the culture has returned to about its original point, 0.5 per cent.

Park and Williams, and also Theobald Smith, have shown that an excess of acid in the medium is detrimental to the production of strong poisons. The rise in acidity above noted amounts to 1 to 1.5 per cent. The reaction of the medium therefore never becomes more acid than 1.5 to 2 per cent, using phenol-phthalin as an indicator. A bouillon which is 1.5 per cent acid to phenol-phthalin is still distinctly alkaline to litmus.

The method as above described has given the best results in this laboratory. With it we have, in one instance, obtained a toxine so strong that 0.0008 c. c. was sufficient to kill standard weight guinea

Medium	Smith's bouillon	Number	5	Date	5.11.04
Meat 3000 gm. Round beef	Water 6000 gm.	Temp.	Refrigerator	Time	24 hours
Filtered through cloth	Amount 6000 gm.	Reaction	2.8	N.NaOH	18. cc.
B. coli stock culture	Amount 60° cc.	Temp.	37° C.	Time	24 hours
Reaction 2.9	Eggs 6 whites	Heated	in open autoclave	20 minutes	
Filtered through paper	Amount 5.560 gm	Water	440 gm.	Reaction	2.2
N.NaOH 102. cc.	Peptone 120 gm.	NaCl	30 gm.	Heated open autoclave	20 minutes.
Reaction 1.6	N.NaOH 66 cc.	Reaction	0.9	N.NaOH	24 cc.
Reaction 0.6	N.NaOH 6 cc.	Reaction	0.5	Glucose	0.1% (except F. tubes)
Filtered through paper	Filled into 7 Fernbach's	4 fermentation tubes	& 50 test tubes.		
Sterilized in autoclave	Temp. 120° C.	Time	20 minutes	Reaction	0.65
Ferm. tubes B. coli	Time 48 hours	Closed arm no growth	Reaction	0.7	
Open arm growth	Reaction	0.7			
Toxin no. 5	Final reaction-test tubes =	0.65			

Fig. 4.—Illustrating record kept of each lot of bouillon.

pigs within four days. We not infrequently obtain toxines, the MLD of which is 0.005 c. c. However, such favorable results are not always obtained. Sometimes for several weeks in succession our toxines have failed to kill guinea pigs in doses as large as 0.01 c. c.

It must be evident to anyone who has had practical experience with the manufacture of diphtheria antitoxin that there are factors concerned in the production of a strong poison that are not at all under-

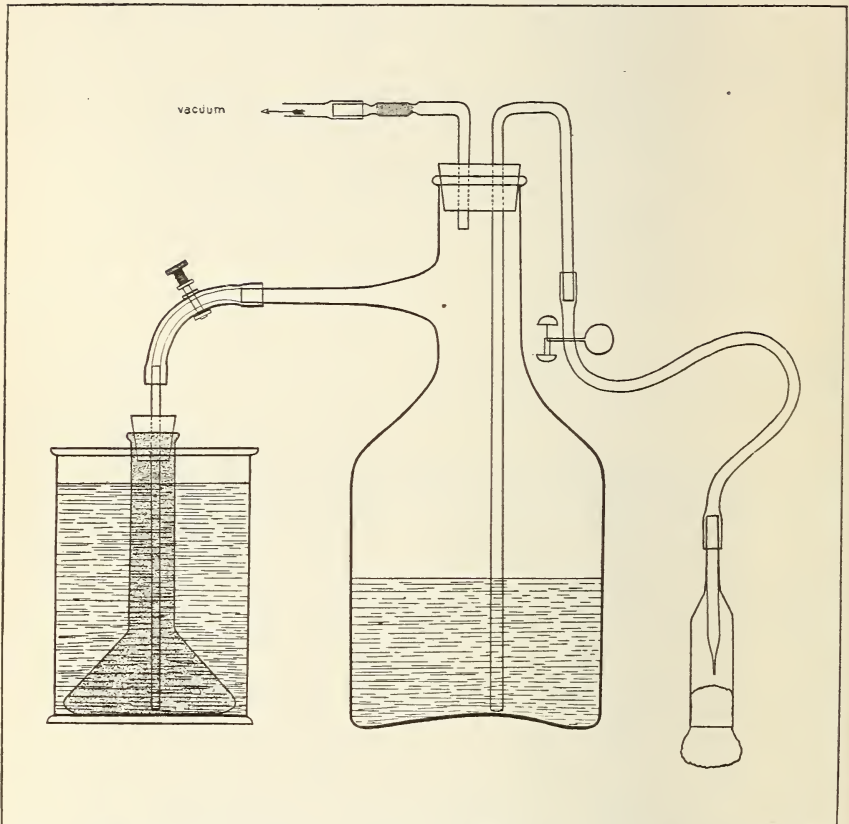


FIG. 5.—Method of filtering the culture. Flask for storing the toxine in bulk with Maesen mouth piece.

stood. It is sometimes discouraging to those who take especial pains to comply with all the requirements believed to favor the production of strong toxines to find that other laboratories who use simpler methods obtain, on the average, poisons of equal and sometimes superior toxicity.

Roux and Yersin<sup>a</sup> noticed that the toxicity of a liquid increased more rapidly and more regularly when the culture is grown in the presence

<sup>a</sup> Macé, E.: *Traité pratique de bactériologie*. pp. 589-590.



of air frequently renewed. They passed filtered air across the surface of the culture. This procedure, once widely employed, has now been generally abandoned, it having been found that it is sufficient to have a large surface of the culture exposed to air. It is now the universal practice in almost all laboratories to grow the toxine in shallow layers of broth contained in flat-bottomed vessels such as the Fernbach flask.

Spronck<sup>a</sup> believed that the presence of glucose in the bouillon prevents the bacillus of diphtheria from producing strong toxic substances. He recommended, in order to eliminate the glucose, to use meat aged almost to the point of putrefaction. He also recommended that care should be taken to use a peptone freed from glucose and the addition to the bouillon of 0.5 per cent of sodium chlorid and a small quantity of carbonate of lime.

Nicolle<sup>b</sup> used fresh beef killed the same morning. He added 2 per cent peptone and 5 per cent salt.

Park and Williams<sup>c</sup> recommend the employment of a decidedly alkaline bouillon, containing 2 to 4 per cent peptone. They obtained the best results with a bouillon distinctly neutral to litmus and then an additional 7 c. c. of normal soda per liter. Such a bouillon has a distinct alkaline reaction to litmus.

Martin<sup>d</sup> insists that the bouillon should be made with a fluid peptone obtained from the stomachs of hogs.

Spronck,<sup>e</sup> in his second process, reported success by growing the culture in a decoction of yeast.

In many laboratories a preference is given for the simplest methods, using an ordinary bouillon distinctly alkaline, following the recommendations of Park and Williams.

The methods used in this laboratory, as previously described, are largely taken from the experimental work of Theobald Smith.

*Neutralization.*—The reaction is taken with phenol-phthalin as an indicator as follows:

To 5 c. c. of the bouillon add 45 c. c. of distilled water plus 1 c. c. of a 0.2 per cent solution of phenol-phthalin in 95 per cent alcohol.

Heat to boiling and titrate while nearly boiling with a  $\frac{N}{20}$  solution of

<sup>a</sup>Spronck: Sur les conditions dont dépend la production du poison dans les cultures diphtériques. Moyen simple de préparer une toxine très active. <Ann. de l'Inst. Pasteur, IX, 1895, p. 758.

<sup>b</sup>Nicolle: Préparation de la toxine diphtérique. <Ann. de l'Inst. Pasteur, 10, 1896, p. 333.

<sup>c</sup>Park & Williams: The production of diphtheria toxin. <Journ. exper. med., I, 1896, p. 164.

<sup>d</sup>Martin: Production de la toxine diphtérique. <Ann. de l'Inst. Pasteur, 12, 1898, p. 26.

<sup>e</sup>Spronck: Préparation de la toxine diphtérique; suppression de l'emploi de la viande. <Ann. de l'Inst. Pasteur, 12, 1898, p. 701.

sodium hydrate. The reaction is indicated by the first appearance of a distinct rose-red color, best seen in a white porcelain dish before a well-lighted window.

Example: 2.6 c. c. of the  $\frac{N}{20}$  NaOH solution is found necessary to neutralize 5 c. c. of the bouillon in order to obtain the desired acidity of 0.5 per cent, add 2.1 c. c. ( $2.6 - 0.5 = 2.1$ ), of the normal soda solution (40 to 1,000) to each 100 c. c. If an acidity of 1.5 per cent is desired, add 1.1 per 100 c. c. ( $2.6 - 1.5 = 1.1$ ).

Each lot of bouillon is numbered and a complete record kept of every stage of the operation upon the blank shown in fig. 6.<sup>a</sup>

The bouillon is distributed in modified Fernbach flasks, presenting a large surface to the air for pellicle growth. Seven hundred and fifty c. c. of the bouillon is placed in each flask.

The freshly prepared media is inoculated upon the surface from a twenty-four-hour-old culture by means of a platinum spoon.

The flasks are incubated for seven days at  $37.5^{\circ}$  C.

They are then removed and examined for purity by means of cover slips. All atypical growths are discarded.

The final reaction of the culture when taken from the incubator is taken for each flask. This usually varies from 0.6 to 0.8 per cent. Very acid results, such as 1.5 or over, would, according to Smith's work, indicate the absence of a strong poison and may be discarded without further testing upon guinea pigs.

The bouillon is now filtered through a pear-shaped, unglazed porcelain filter or a Berkefeld candle by means of a vacuum. The arrangement for filtering the virus is shown on page 38. This diagram also illustrates the character of the flask used to store the toxine in bulk. It is very convenient to draw off small amounts from time to time by means of the siphon and Maasen nozzle without danger of contamination. The especially strong and otherwise suitable toxines are bottled from these flasks without the addition of any preservative.

*Bottling and preserving.*—The toxine is kept in bulk in the 2 liter bottle shaped flasks described above, and later divided into small ground-glass stoppered bottles holding 5 and 10 c. c. each.

The small bottles are filled to the neck with the toxine and the stopper inserted so that the air is all displaced and the fluid completely fills the vial.

A minute quantity of sterilized liquid petrolatum is touched to the ground glass of the stopper so as to prevent the two surfaces of glass

<sup>a</sup>I am indebted to Dr. Herbert D. Pease, director of the antitoxin laboratory, New York State department of health, for suggestions on the method of keeping records on the card system shown in figs. 4 and 6. Doctor Pease very kindly let me have blanks used by him, which were modified to suit our purposes.

Toxin	Diphtheria	Number	5	Date	5-14-04	Amount	4 x 750 = 3000 cc.
Medium	Bouillon no. 5	Reaction	0.65	Muscle sugar	none	Dextrose	0.1%
Culture	Park no. 8	Medium	Smith's bouillon	Temp.	37° C.	Age	24 hours
Date inoc.	5-14-04	Temp.	37.5° C.	Pellicle	heavy +	Entire	in 48 hours
"	remov. 5-21-04	Reaction	$\left. \begin{array}{l} \text{2.7} \\ \text{3.1} \\ \text{3.6} \end{array} \right\} \begin{array}{l} \text{1.7} \\ \text{1.7} \\ \text{1.6} \end{array}$	Amount	2 L	Preservative	none
	Filtered through porcelain		5-21-04	<p>Stored at room temperature for 10 days; then at 15° C., Bottled 6-3-04 and stored at 5° C.</p>			
Dates tested	Animals	Tested for	Result				
5-26-04	G.P. # 9	M.L.D.	.005	Death	1 day	18 hours	
"	" 10	"	.005	"	1 "	20 "	"
5-31-04	" 13	"	.004	"	3 "	12 "	"
"	" 12	"	.003	"	2 "	12 "	"
"	" 11	"	.002	"	4 "	0 "	"
7-21-04	" 105	"	.001	"	5 "	5 "	"
"	" 107	"	.0008	"	7 -	23 "	"
9-30-04	" 311	"	.002	"	4 "	3 "	"
12-15-04	" 1030	"	.002	"	4 "	8 "	"

FIG. 6.—Illustrating record kept of each toxine.

sticking to each other. As it is probable that some of these bottles will be kept for years, this may be an important detail. The neck of the bottle is carefully dried and then quickly dipped into melted paraffin with a high melting point so as to seal the joint completely and prevent evaporation or contamination.

Each bottle is labeled and stored in a special ice box kept at a constant temperature of  $5^{\circ}$  C.

It will be seen that according to this method the toxine is kept in absolute darkness, free from contact with the oxygen of the air, and at an equable and low temperature. By the use of the ordinary bacteriological precautions the addition of a preservative as toluol and similar substances is rendered unnecessary.

#### TESTING THE TOXINE.

It is first necessary to determine the minimal lethal dose of the toxine with approximate accuracy. Weak poisons are discarded. A fresh toxine requiring more than 0.01 c. c. to kill a 250-gram guinea pig is too weak for the purposes of this special work.

If the preliminary tests show that the poison has the required toxicity, its minimal lethal dose must then be accurately determined. This may require a number of animals.

After the absolute toxicity of the poison has been determined it is necessary to establish the  $L+$  and the  $L^0$  doses. An illustration of how these doses are obtained follows. These results are taken from our records.

#### *Tests to determine the $L+$ dose of toxine No. 7.*

	Result.
1 immunity unit + 0.19 c. c. toxine .....	Invariably causes late paralysis, never acute death.
1 immunity unit + .20 c. c. toxine .....	Sometimes causes late paralysis and sometimes acute death.
1 immunity unit + .21 c. c. toxine .....	Always causes acute death about the fourth day.
1 immunity unit + .22 c. c. toxine .....	Always causes acute death, usually on the second or third day.

The  $L+$  dose of this toxine is, therefore, just 0.21 c. c.



*Tests to determine the L<sup>o</sup> dose of toxine No. 7.*

	Result at autopsy forty-eight hours after inoculation.
1 immunity unit + 0.14 c. c. toxine.....	No visible reaction.
1 immunity unit + .15 c. c. toxine.....	No visible reaction.
1 immunity unit + .16 c. c. toxine.....	Slightest possible congestion about carbon particles, or no reaction.
1 immunity unit + .17 c. c. toxine.....	Apparent reaction at site of inoculation.
1 immunity unit + .18 c. c. toxine.....	Injection and edema at site.
1 immunity unit + .19 c. c. toxine.....	Injection and edema at site.

The L<sup>o</sup> dose of this toxine, therefore, is 0.16 c. c.

These figures are actual results obtained with our toxine No. 7.

If the interval between the L+ and the L<sup>o</sup> dose is greater than 15 × MLD, the toxine contains too great a proportion of toxones, etc., and should not be used for testing the strength of antitoxin. If it were possible to obtain ideally pure toxines in which the interval between the L+ and the L<sup>o</sup> dose was only one minimal lethal dose, our problem would be simplified. Unfortunately such a poison has only once been demonstrated. However, by these preliminary tests upon a number of poisons we select the most suitable for the purposes of this special work.

Having selected a suitable poison, it is now laid aside to season. For this purpose the toxine should be kept in bulk, so that the process will be uniform throughout the mixture. If it is kept in diffused light at room temperature, the changes will take place quicker than if kept in the ice box. At intervals of about a month the toxine is tested in order to determine the rate of change. These examinations will disclose the fact that the toxicity gradually diminishes and the L+ dose increases. These alterations take place progressively until the poison arrives at a stage of equilibrium. Here it may remain for a long time. A short time before this stage of equilibrium is reached it is best to divide the toxine into small bottles, excluding the air, in order to guard against loss by accident or contamination, and store the entire lot in a cold place protected from light.

The toxine can not be depended upon for the purpose of testing the antitoxin until this stage of equilibrium is reached. After a varying length of time the toxine will again show change in toxicity, and when this second period of change sets in the toxine should be discarded as no longer serviceable for the purposes of these tests.

As soon as the toxine has reached its stage of stability or equilibrium, that is, when the test dose remains constant, it is necessary to determine this test dose (L+) with the greatest possible accuracy.

The well-standardized toxines used in this laboratory are tested

against the immunity unit every week or two in order to assure ourselves that they are not undergoing change. A number of carefully tested toxins are always kept on hand, so that we may have a double test of the serums we are standardizing, as well as to guarantee against changes in the toxins which may set in suddenly.

The exact standardization of a toxin takes considerable time and we therefore can not depend upon one poison. The exact L+ dose of a well-seasoned toxin is the keynote of the whole testing operation. Without this test dose good results are impossible. Every effort must be made to obtain a reliable poison that answers all the requirements and, having such a toxin, to maintain it under the most careful conditions in order to keep it in a state of equilibrium as long as possible. As the toxin grows old the tests naturally multiply in number and increase its reliability for the purpose of determining the unit strength of antitoxins.

On account of the importance of the L+ dose I exhibit here a series of L+ tests showing the character of the results obtained by the poison after it has gained its stage of equilibrium.

*Table giving the results of tests on Toxine No. 7 for L+ dose, using 0.21 c. c. of the toxin against one immunity unit, from October 24, 1904, to December 22, 1904.*

Guinea pig No.	Time of death.	Remarks.	Guinea pig No.	Time of death.	Remarks.
	<i>Dys. hrs.</i>			<i>Dys. hrs.</i>	
395.....	3 0		859.....	2 20	Usual reactions.
453.....	3 5		860.....	2 15	Do.
454.....	5 15		903.....	3 7	
544.....	3 9		904.....	3 16	
545.....	3 21		905.....	6 2	
546.....	3 5		948.....	3 2	
547.....	3 18		949.....	3 2	
601.....	5 16		950.....	3 18	
602.....	2 17	Clear serous fluid in pleural cavities.	951.....	3 18	
			984.....	3 6	
603.....	3 13		985.....	1 18	Pneumonia.
604.....	3 6		986.....	1 17	Peritonitis; serous exudate; omentum very red.
605.....	1 18	Omentum, mesentery, and broad ligament injected, etc.	987.....	5 6	
			988.....	1 17	Pneumonia.
621.....	3 2		989.....	2 6	Clear serum in pleural cavities.
622.....	2 19	Clear fluid in pleural cavity.	1063.....	4 20	
623.....	3 2		1064.....	3 0	
624.....	3 14		1065.....	3 12	
625.....	3 7		1066.....	4 13	
693.....	3 18		1067.....	3 8	
694.....	4 11		1068.....	3 4	
695.....	3 14		1069.....	1 17	Pneumonia, both upper lobes.
696.....	4 8		1124.....	2 17	Spleen and liver show sharply defined caseous areas.
697.....	3 16				
750.....	3 19		1125.....	4 16	
751.....	2 12	Peritoneum discolored and petechiæ throughout.	1126.....	3 17	
			1127.....	5 17	
752.....	2 12	Some peritoneal reaction and clear serum in pleurae.	1128.....	2 17	Usual reaction.
			1129.....	3 6	
753.....	2 14	Nothing unusual, adrenals congested, local reaction.	1150.....	3 8	
			1151.....	1 19	Severe peritoneal reaction.
		Do.	1152.....	2 17	Peritoneal fat injected.
754.....	2 17		1153.....	3 11	
808.....	3 17		1154.....	2 16	Clear serum in pleural cavities.
809.....	4 14				
855.....	2 20	Usual reaction.	1155.....	2 12	Usual reaction.
856.....	4 4		1156.....	3 11	
857.....	3 9				
858.....	4 4				

During two months covered by the table every one of the 68 animals injected with 0.21 c. c. of this toxine, mixed with 1 immunity unit, died acutely. None recovered. Most of the guinea pigs died on the fourth day. As we usually inoculate our animals at about 3 o'clock in the afternoon, animals dying between three days two hours and four days two hours will appear on the autopsy table on the fourth day.

Animals dying before the fourth day usually show at autopsy some reason for this increase of susceptibility.

The following tables used for diluting our toxines for MLD and L+ doses will be found useful:

*TABLES FOR DILUTING TOXINES FOR MLD.*

*First dilution.*

$$1+99=1:100$$

*Second dilution.*

1 of first dilution+49=1: 5000	1 c. c.=.0002
	1.5 c. c.=.0003
	2 c. c.=.0004
	2.5 c. c.=.0005
	3 c. c.=.0006
1 of first dilution+39=1: 4000	0.8 c. c.=.0002
	1 c. c.=.00025
	1.2 c. c.=.0003
	1.6 c. c.=.0004
	2 c. c.=.0005
	2.4 c. c.=.0006
	2.8 c. c.=.0007
	3.2 c. c.=.0008
1 of first dilution+29=1: 3000	0.9 c. c.=.0003
	1 c. c.=.00033
	1.2 c. c.=.0004
	1.5 c. c.=.0005
	1.8 c. c.=.0006
	2.1 c. c.=.0007
	2.4 c. c.=.0008
	2.7 c. c.=.0009
	3 c. c.=.001
1 of first dilution+9=1:1000	1. c. c.=.001
	1.5 c. c.=.0015
	2 c. c.=.002
	2.5 c. c.=.0025
	3 c. c.=.003

## TABLES FOR DILUTING TOXINES FOR MLD.—Continued.

*First dilution.*

$1+49=1:50$

*Second dilution.*

1 of first dilution	+9=1:500	1	c. c.=.002
		1.5	c. c.=.003
		2	c. c.=.004
		2.5	c. c.=.005
		3	c. c.=.006

*First dilution.*

$1+29=1:30$

*Second dilution.*

1 of first dilution	+9=1:300	0.9	c. c.=.003
		1	c. c.=.0033
		1.05	c. c.=.0035
		1.2	c. c.=.004
		1.35	c. c.=.0045
		1.5	c. c.=.005
		1.65	c. c.=.0055
		1.8	c. c.=.006
		1.95	c. c.=.0065
		2.1	c. c.=.007
		2.25	c. c.=.0075
		2.4	c. c.=.008
		2.55	c. c.=.0085
		2.7	c. c.=.009
		2.85	c. c.=.0095
		3	c. c.=.01

$1+99=1:100$	1	c. c.=.01
	1.5	c. c.=.015
	2	c. c.=.02
	2.5	c. c.=.025
	3	c. c.=.03

$1+49=1:50$	1	c. c.=.02
	1.5	c. c.=.03
	2	c. c.=.04
	2.5	c. c.=.05
	3	c. c.=.06



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 TABLES FOR DILUTING TOXINES FOR MLD.—Continued.
 

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1+29=1:30	.9	c. c.=.03
	1.2	c. c.=.04
	1.5	c. c.=.05
	1.8	c. c.=.06
	2.1	c. c.=.07
	2.4	c. c.=.08
	2.7	c. c.=.09
	3	c. c.=.1

---

 TABLES FOR DILUTING TOXINES FOR L+ DOSE.
 

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1+19=1:20	1	c. c.=.05
	1.1	c. c.=.055
	1.2	c. c.=.06
	1.3	c. c.=.065
	1.4	c. c.=.07
	1.5	c. c.=.075
	1.6	c. c.=.08
	1.7	c. c.=.085
	1.8	c. c.=.09
	1.9	c. c.=.095
	2	c. c.=.1
	2.1	c. c.=.105
	2.2	c. c.=.11
	2.3	c. c.=.115
	2.4	c. c.=.12
	2.5	c. c.=.125
	2.6	c. c.=.13
	2.7	c. c.=.135
	2.8	c. c.=.14
	2.9	c. c.=.145
	3	c. c.=.15

---

1+9=1:10	1	c. c.=.1
	1.05	c. c.=.105
	1.1	c. c.=.11
	1.15	c. c.=.115
	1.2	c. c.=.12

## TABLES FOR DILUTING TOXINES FOR L+ DOSE—Continued.

---

1+9=1:10	1.25 c. c. = .125
	1.3 c. c. = .13
	1.35 c. c. = .135
	1.4 c. c. = .14
	1.45 c. c. = .145
	1.5 c. c. = .15
	1.55 c. c. = .155
	1.6 c. c. = .16
	1.65 c. c. = .165
	1.7 c. c. = .17
	1.75 c. c. = .175
	1.8 c. c. = .18
	1.85 c. c. = .185
	1.9 c. c. = .19
	1.95 c. c. = .195
	2 c. c. = .2
	2.05 c. c. = .205
	2.1 c. c. = .21
	2.15 c. c. = .215
	2.2 c. c. = .22
	2.25 c. c. = .225
	2.3 c. c. = .23
	2.35 c. c. = .235
	2.4 c. c. = .24
	2.45 c. c. = .245
	2.5 c. c. = .25
	2.55 c. c. = .255
	2.6 c. c. = .26
	2.65 c. c. = .265
	2.7 c. c. = .27
	2.75 c. c. = .275
	2.8 c. c. = .28
	2.85 c. c. = .285
	2.9 c. c. = .29
	2.95 c. c. = .295
	3 c. c. = .3

---

## TABLES FOR DILUTING TOXINES FOR L+ DOSE—Continued.

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1+4=1:5	1	c. c. = .2
	1.1	c. c. = .22
	1.2	c. c. = .24
	1.3	c. c. = .26
	1.4	c. c. = .28
	1.5	c. c. = .3
	1.6	c. c. = .32
	1.7	c. c. = .34
	1.8	c. c. = .36
	1.9	c. c. = .38
	2	c. c. = .4
	2.1	c. c. = .42
	2.2	c. c. = .44
	2.3	c. c. = .46
	2.4	c. c. = .48
	2.5	c. c. = .5
	2.6	c. c. = .52
	2.7	c. c. = .54
	2.8	c. c. = .56
	2.9	c. c. = .58
	3	c. c. = .6

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1+1=1:2	1	c. c. = .5
	1.1	c. c. = .55
	1.2	c. c. = .6
	1.3	c. c. = .65
	1.4	c. c. = .7
	1.5	c. c. = .75
	1.6	c. c. = .8
	1.7	c. c. = .85
	1.8	c. c. = .9
	1.9	c. c. = .95
	2	c. c. = 1

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## THE ANTITOXIN.

*Preparation.*—The antitoxic serum was prepared at Parke, Davis & Co., Detroit, Mich., by Passed Asst. Surg. John F. Anderson, Assistant Director of the Hygienic Laboratory.

Two horses were selected which had furnished a reliable high potency serum. These horses had been treated in the usual manner by gradually increasing doses of the diphtheria toxine.

From horse No. 781 six liters of blood were drawn on June 14, 1904, at 9 a. m. The blood was drawn into 12 large test tubes, each tube containing approximately 500 c. c. Immediately after bleeding the blood was placed in a room, the temperature of which was about 25° C.

The next day, June 15, at 8.30 a. m., the horse was again bled for 6 liters, also into 12 tubes. This blood was placed with the lot drawn on the 14th.

After the blood had been clotted several days the clear serum was poured from the 24 tubes into a special bottle. Only that serum which was perfectly clear and entirely free from coloring matter was used. As the serum did not separate from this blood as clearly as usual, only 1,378 c. c. of serum were obtained from the 24 tubes. The serum was at once examined for potency and found to contain approximately 500 units. It was also tested bacteriologically for purity and no growths were obtained in bouillon tubes. After the samples were taken for testing, 20 c. c. of pure chloroform were put into the bottle with the serum, which was then at once placed in the ice chest at a temperature of 1.7° C. Chloroform was added to the serum to prevent any possible contamination. All of it of course disappeared with the vacuum under the drying process.

On June 22 evaporation of the serum was accomplished by bubbling dry air through the serum with a moderate vacuum. The vacuum varied from 20 to 23 inches. The arrangement for drying the serum is well shown in the accompanying illustration (fig. 7). The serum was syphoned into the large drying tube in small quantities, and the warm air bubbling through rapidly dried it and at the same time prevented the formation of hard cakes. The water bath surrounding the tube containing the serum was kept at about 35° C.; it varied from 32° to 36° C. throughout the operation. The temperature of the dry



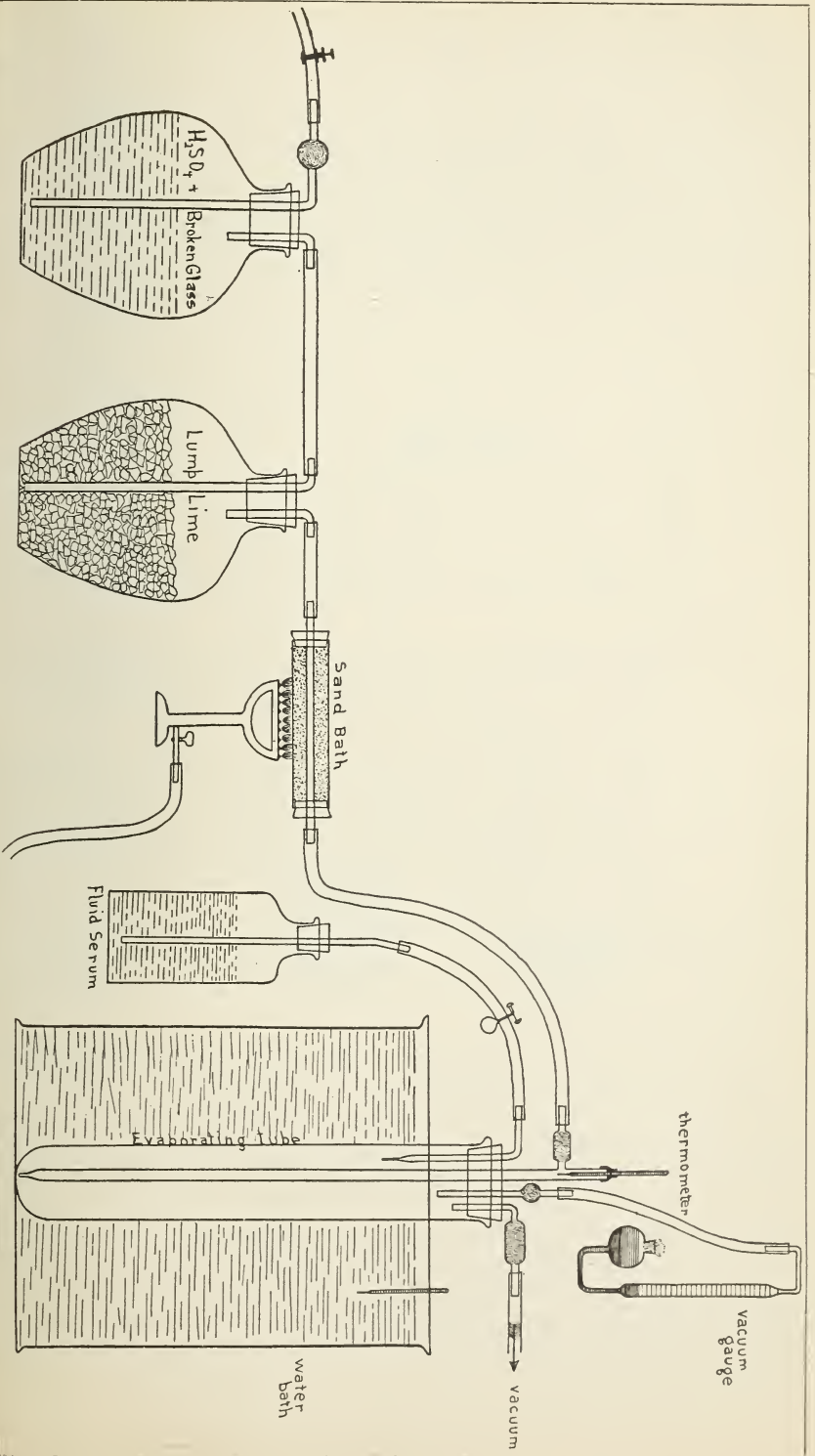


Fig. 7.—The apparatus used in evaporating the serum to dryness.

air passed through the serum was kept as nearly as possible at  $33^{\circ}$  C.; it never exceeded  $35^{\circ}$  C. The evaporation proceeded with fair rapidity. At the beginning there was some frothy bubbling, but that soon subsided. The entire lot of serum was dried in ten and a half hours, drying in large sugar-like flakes. Very little adhered to the side of the tube and there were no hard cakes.

The dried serum weighed 25 grams and was readily powdered in a sterile mortar to break up the larger lumps and then placed in a special porcelain grinder with porcelain balls and rotated for several hours. About half a gram of the powdered serum was planted in a tube of bouillon, which showed no growth at the end of four days.

Horse No. 590: This horse was also bled on two succeeding days—June 20 and 21—six liters being taken at each bleeding, as before. The 24 tubes, each containing half a liter of blood, were placed in a room with a temperature of approximately  $25^{\circ}$  C. After clotting two days the serum was poured off, only the perfectly clear fluid entirely free from coloring matter being retained. From the 12 liters of blood, 4,127 c. c. of serum were obtained. Samples were at once taken and tested for purity and potency, as before, with satisfactory results.

As soon as the samples were taken, 40 c. c. of pure chloroform were placed in the bottle with the serum, which was placed in the ice box at  $1.7^{\circ}$  C. Upon the same day evaporation of the serum was begun, proceeding as above described.

The evaporation of this amount of serum required 25 hours, the temperature of the air and water bath being the same as before. This serum dried in large golden-colored flakes, which were partly powdered in the sterile mortar and then put into the ball grinder and reduced to a fine, almost impalpable powder.

Four hundred and five grams of the dried serum were obtained. Half a gram was planted into bouillon, which showed no growth in three days, indicating that it had remained free from contamination throughout the operation.

*Bottling and preserving the serum.*—The dried serum must be kept guarded under special conditions to prevent deterioration. The oxygen of the air must be excluded in order to retard the process of oxidation, which rapidly alters the antibodies, especially under the influence of light. The serum is, therefore, always kept in absolute darkness.

The serum must be perfectly dry. It is therefore kept under the influence of phosphoric anhydrid, ( $P_2O_5$ ), as shown in the accompanying illustration (fig. 8). Further, the serum is kept in a specially built ice box, maintained at a constant temperature of  $5^{\circ}$  C. by means of circulating brine.

The little bulbs in which the serum is preserved, shown in fig. 8, are made of amber glass. The following method is used in filling and sealing these bulbs:

Cotton is first introduced in the neck as far as the constriction. Then about 1 gram of phosphoric anhydrid is placed in one of the bulbs. The neck through which the acid has entered the little apparatus is now sealed off by the blowpipe. Then about 1.2 grams of the dried serum are placed in the other bulb. The neck, from the

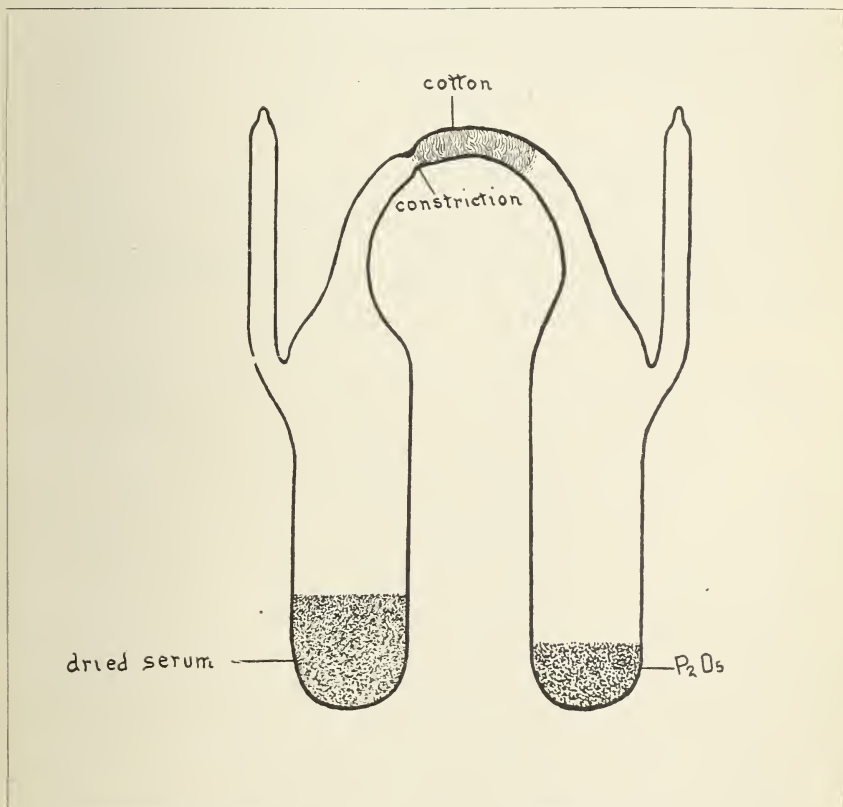


FIG. 8.—U-shaped tubes used for preserving the standard serum. Exact size.

serum side, is connected with a vacuum apparatus, and as soon as the vacuum is sufficiently high this is also hermetically sealed.

Each bulb is now sealed in a black box, which excludes the light, and is kept in the ice box at 5° C., as before stated.

From this arrangement it will be seen that the powdered serum is kept dry, free from contact with the oxygen of the air, guarded against the action of light, and preserved at a constant low temperature.

*Dissolving the dried serum.*—Once every two months, or whenever it is desired to test the serum, one of these bulbs is broken and 1 gram of the serum carefully weighed and dissolved in physiological salt solution (0.85) one part, Price's glycerin two parts.

*Testing.*—This glycerinated solution of blood serum is now accurately standardized in order to determine its precise antitoxic value in terms of Ehrlich's immunity unit.

The number of immunity units contained in a given quantity of the serum is determined by the test (L+) dose of toxine.

That quantity of serum necessary to add to the L+ dose of the toxine so that the mixture will kill the guinea pig on about the fourth day contains just one immunity unit. In the commercial testing of serums in order to have a coefficient of safety it would be safer to require the pig to live.

We use a number of toxines, the L+ doses of which have been very painstakingly ascertained on a large number of animals. The details of the technique by which this part of the testing is carried out will be found under the caption "Methods used in making the unit," and need not be repeated here.



## THE METHODS USED IN MAKING THE UNIT.

*The glassware.*—The glassware employed in making the immunity unit for standardizing toxines and antitoxins is used for no other purpose. To a certain extent the glassware used for measuring and diluting the toxines is kept separate from that used for the serums.

The pipettes, burettes, graduated flasks, and mixing cylinders have been carefully calibrated or standardized by the Bureau of Standards, to whom we are under many obligations, not only for this work but for suggestions as to the most accurate methods of measuring precise amounts of fluids.

So far as possible all measurements are made with "capacity" instruments. "Outflow" instruments, made "to deliver" given quantities, are only used in the measurements of the final dilutions, in which case it is evidently impossible to use capacity pipettes.

The glassware used for the purposes of this special work has been calibrated with particularly fine graduations that pass halfway or all the way around the pipette, burette, or neck of the flask.

The diluting fluid is measured in mixing cylinders of a particular design made for me by Messrs. F. & M. Lautenschläger, of Berlin, Germany. Two of these mixing cylinders are shown in fig. 9. We have a series of these cylinders, each measuring quantities in intervals of 10 c. c. up to 100 c. c. The first set of cylinders is graduated to contain from 0 to 10 c. c., the next size from 10 to 20 c. c., then 20 to 30 c. c., 30 to 40 c. c., and finally 90 to 100 c. c. It will be noticed by the illustration that these mixing cylinders are subdivided into tenths, which makes it possible to measure our diluting fluid with great accuracy. It will also be seen that the cylinders have neither neck nor shoulder, and that the ground-glass stopper fits directly into the cylinder without a constriction. The internal diameter of these cylinders is just 12 mm., which readily permits the introduction of any one of our pipettes. The smaller pipettes average 6 to 8 mm. in outside diameter; the larger ones do not exceed 10 mm. Attention is also invited to the fact that the shape of the cylinders readily allows thorough mixing and cleansing.

We also use a style of mixing flask, shown in fig. 10, which was made for me by the Arthur H. Thomas Company, Philadelphia, Pa. The smaller flask is graduated to contain 49 and 50 c. c.; the larger flask is graduated to contain 98, 99, and 100 c. c. As we have frequent occasion to use these quantities, the flasks are particularly convenient on account of their simplicity and comparative cheapness. It will be noticed that the neck has no shoulder, or constriction.

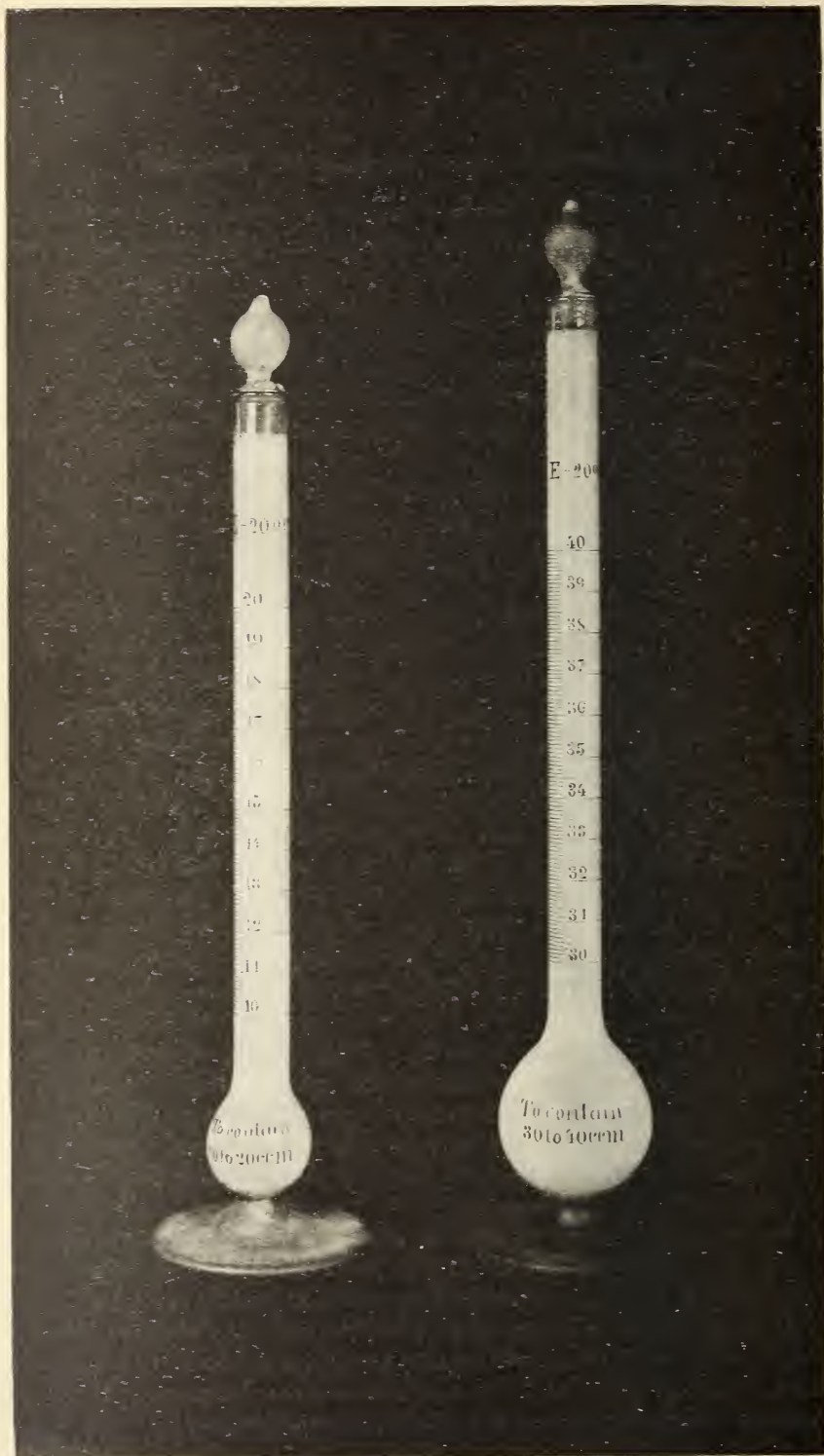


FIG. 9.—Special pattern mixing flasks for measuring toxins and serum dilutions.



FIG. 10.—Capacity flasks for measuring dilutions of toxine, etc.

In reading the proper height of the fluid in these flasks the bottom of the meniscus is brought just to the line. By holding a black surface, such as a piece of cloth, beneath the level of the fluid the reflection makes the surface of the fluid stand out clearly as a single curved line, doing away with the annoying reflections that otherwise prevent accurate readings. This black curve of the meniscus is best seen against a white background.

The use of the "meniscus visir blende" of Doctor Göckel greatly facilitates the accurate reading of burettes, pipettes, and flasks. This little apparatus is exceedingly simple. It may be improvised in any laboratory, and will be found very useful.

All the glassware used in this work is cleaned by first flushing with cold, then with hot water, in order to remove the gross dirt. It is then bathed in a saturated solution of bichromate of potassium in concentrated sulphuric acid. The glassware is now flushed with tap water until all the acid is removed, when it is finally rinsed in several changes of distilled water and allowed to dry in the air.

All glassware is sterilized by heat at 125° C. for one hour, and kept under the usual precautions to prevent bacterial contaminations.

All the glassware used in this work has been standardized to contain or to deliver fluids at 20° C. instead of 15° C., because the former more nearly approaches the usual room temperature in this climate. The serums and toxins are removed from the ice chest a sufficient time before using to allow them to stand (in the dark) until they approach the room temperature before they are measured out.

*The diluting fluid.*—We use "physiological" salt solution (0.85 per cent. sodium chlorid C. P.) as our diluting fluid for all toxins, serums, etc. This salt solution is made up in bulk with distilled water and sterilized by steam. It is always used at room temperature.

*Bacteriological precautions.*—All the work is done under the usual bacteriological precautions to prevent contamination. We do not observe the extreme precautions necessary to obtain a pure culture of an organism. The toxin and antitoxin are of course kept under perfectly sterile conditions and all the glassware with which they come into contact is clean and sterile, which appears sufficient to prevent contaminations entering the work that would affect the results. The autopsies made in this laboratory have so far failed to reveal any such infections of the guinea pig. Cultures were made from 154 consecutive guinea pigs. Some of the heart's blood was inoculated into bouillon tubes. Of these tubes 108 remained sterile; growth appeared in 46, as follows:

A coccus in .....	20
Motile bacillus in .....	18
Nonmotile bacillus in .....	5
Coccus and bacillus in .....	3



A study of the histories of the guinea pigs showing the presence of bacteria in the blood disclosed the fact that most of them were probably either terminal or post-mortem infections.

#### METHOD OF USING THE PIPETTES.

In order to obtain accurate results with pipettes it is important to use them in the same way that they have been calibrated. This applies both to pipettes which have been graduated "to deliver" a given volume as well as to pipettes graduated "to contain" a given volume. If the method by which the pipettes were graduated can not readily be obtained from the firm making them, it will be necessary to restandardize them to determine several points.

With delivery pipettes it is essential to know whether they are to be used by blowing out the last drop or by touching the point of the pipette to the surface in order to remove the last drop that adheres to the tip.

The time allowed for drainage, after the pipette is emptied, varies with the rate of flow and also with the standard methods used by different countries.

It is furthermore very important in accurate work to know whether pipettes have been graduated in accordance with the Mohr liter or the true (French) liter.

The Mohr liter is the volume occupied by 1 kilogram of pure water at  $17.5^{\circ}$  C., weighed in air against brass weights, the air being under normal pressure and at  $17.5^{\circ}$  C. The volume of such a liter is 1,002.36 c. c.

The true or so-called French liter is the volume occupied by 1 kilogram of pure water at  $4^{\circ}$  C., the weighing being reduced to a vacuum. The volume of the true liter may be assumed equal to 1,000 c. c.

Volumetric apparatus is for convenience usually graduated to contain or to deliver true cubic centimeters at higher temperatures than  $4^{\circ}$  C., namely, at  $15^{\circ}$ ,  $17.5^{\circ}$ , or  $20^{\circ}$  C., the standard temperature being marked upon the apparatus. The differences between apparatus graduated on the true and on the Mohr systems are as follows:<sup>a</sup>

If standard at  $15^{\circ}$ , Mohr apparatus is larger by 2.30 c. c. per liter.

If standard at  $17.5^{\circ}$ , Mohr apparatus is larger by 2.36 c. c. per liter.

If standard at  $20^{\circ}$ , Mohr apparatus is larger by 2.42 c. c. per liter.

In ordinary rough-and-ready work all these refinements may be disregarded, but in certain determinations requiring great precision a neglect of these details may cause serious error.

These matters were brought forcibly to my attention in the work of making the standard unit for diphtheria antitoxin.

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<sup>a</sup>I am indebted to Dr. L. A. Fischer, Chief of the Division of Weights and Measures, Bureau of Standards, for these figures.

The errors in using pipettes may be especially manifest in measuring solutions of higher density or greater viscosity than water. In fact it is quite impossible to obtain even approximately correct results in measuring such solutions as glycerin, blood serum, etc., from delivery pipettes. This fact led Ehrlich to use the capacity pipettes of von Leybold in measuring these substances in making his unit for diphtheria antitoxin.

I have found the methods which I shall now describe very useful in the accurate work necessary in making a Government standard and believe their simplicity and accuracy will commend them to others.

*Method of using capacity pipettes.*—The pipettes are fitted with a rubber bulb at their upper end and held in an ordinary retort stand, as may be seen by reference to the illustration (fig. 12).

The rubber bulb is clamped between the jaws of the compressor. The fluid is drawn up into or expelled from the pipette by tightening or loosening the screw. By this means we have an absolute control over the height of the column of fluid in the pipette. The rubber bulb takes the place of the suction usually applied by the mouth and is used both to fill and to empty the pipette.

In using, the free end of the pipette is immersed into the fluid to be measured, and by loosening the screw the column of fluid is gradually brought approximately to the mark. The operation is repeated once, or twice so as to wash the pipette with the fluid to be measured, which is finally drawn a little above the graduation mark. Care must be taken not to wet the interior of the pipette at any time during the process of measuring more than 1 to 2 mm. above this mark, because the extra wetted surface would furnish an appreciable error. By holding the pipette in the retort stand and using the rubber bulb as shown, such accidents are much less likely to happen than is the case when the mouth is used to suck the fluid up and down.

The outside of the pipette is now carefully wiped with a few thicknesses of sterile gauze. Then by placing the gauze to the free end of the pipette the column of liquid may be slowly drawn down until the meniscus rests directly upon the line.

The contents of the pipette are now emptied into the diluting fluid, which has previously been measured out, and the pipette must be washed out thoroughly by drawing the fluid up and down several times, again using the rubber bulb for this purpose.

The flask containing the dilution is now agitated so as to obtain a uniform mixture of solution, and the pipette is again washed in and out so that the fluid which adheres to and remains in the pipette is the same dilution as the mixture in the flask. A larger quantity of dilution is always made than required, so that aliquot parts will represent very definite quantities of the original substances.

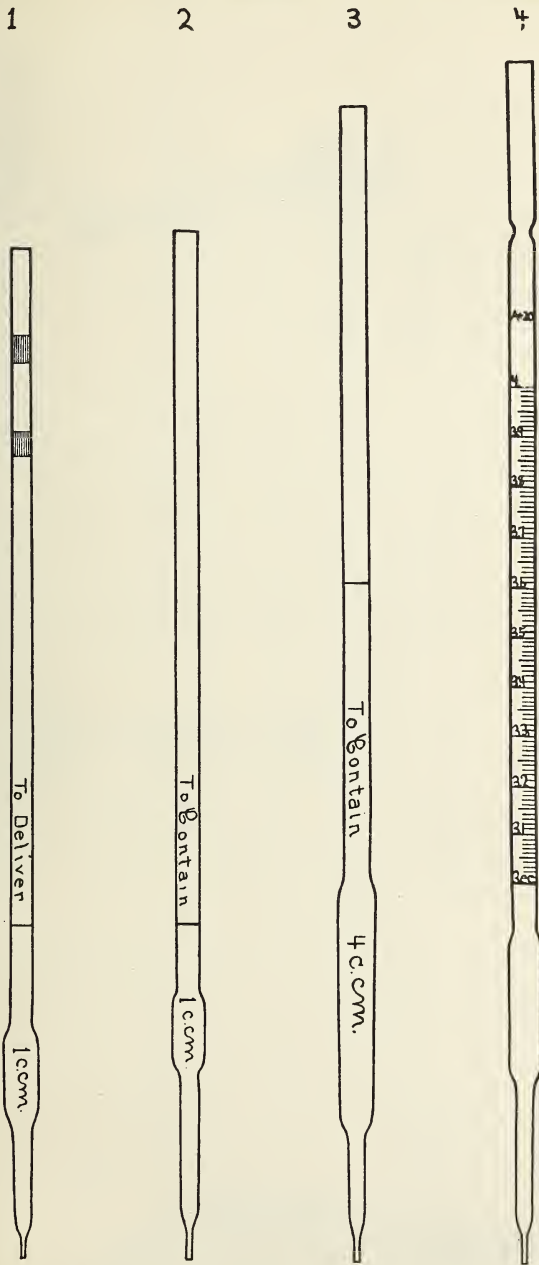
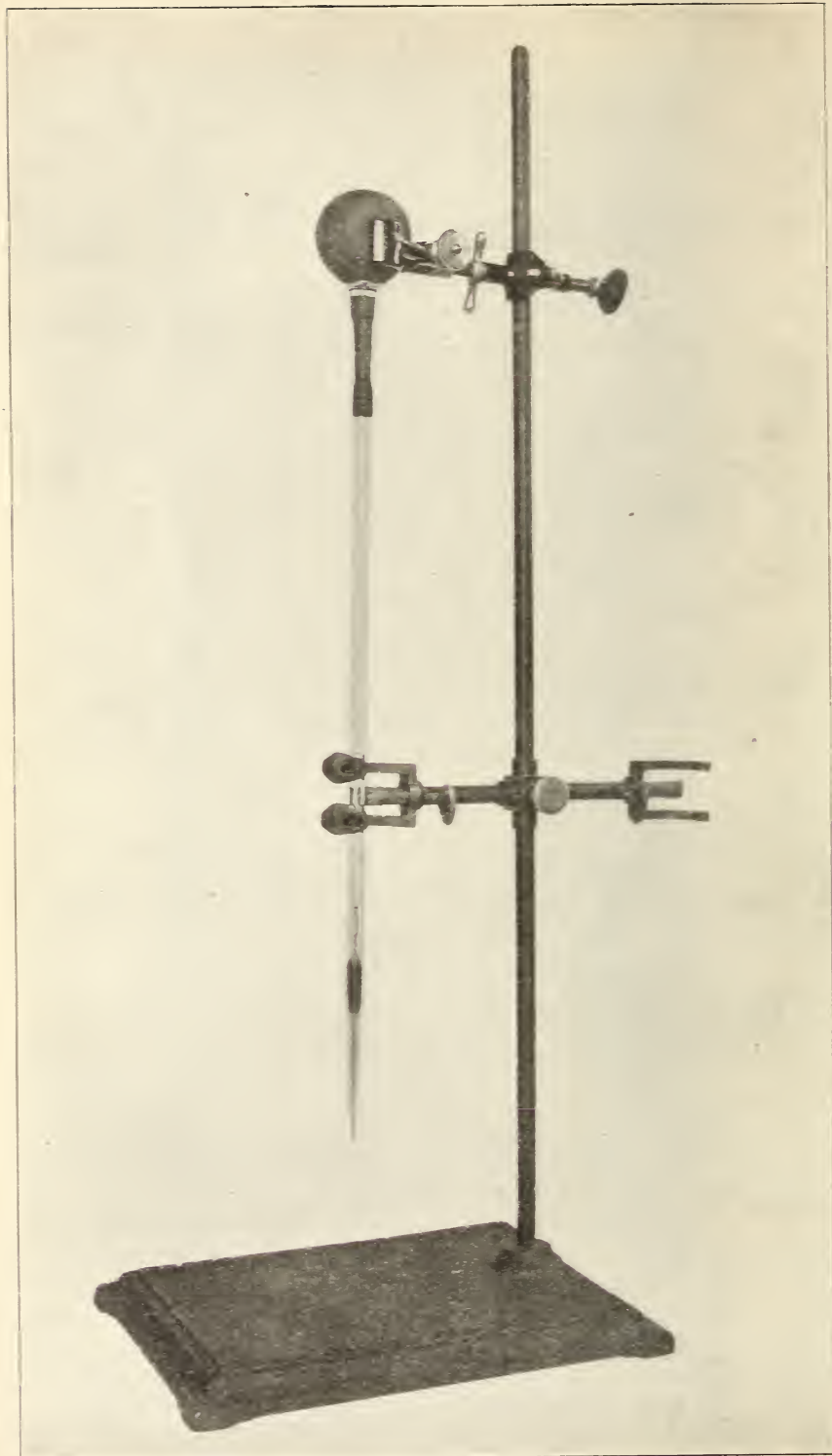


FIG. 11.—Various pipettes used in the work. 1. A delivery pipette, with two etched bands for ready identification, graduated to blow out the last drop. 2. A 1 c. c. capacity pipette. 3. A 4 c. c. capacity pipette. 4. An Ehrlich delivery pipette graduated in hundredths.





The whole process does not take as long as the telling, and is much quicker and more accurate than the ordinary method of using the pipettes with a free hand.

*Method of using delivery pipettes.*—The method of using “outflow” or “delivery” pipettes differs materially from that of using capacity pipettes.

The rubber bulb is attached to the pipette as before, but in this case there is a T between the bulb and the pipette. From this T a small piece of rubber tubing, controlled by a pinchcock, is located, as may be seen by reference to fig. 13.

The pinchcock is kept closed while the pipette is filled to the proper graduation, which is accomplished just as in the case of the capacity pipettes described above.

By opening the pinchcock the contents of the pipette are allowed to flow out. When the last drop that will flow out of its own accord escapes, the proper time is allowed to elapse for drainage and the point of the pipette touched to the surface. By this procedure a very constant quantity of fluid remains in the capillary tip of the pipette.

If the pipettes have been standardized to blow out this last drop, this may be done conveniently by closing the pinchcock and compressing the rubber bulb.

The soft rubber ear syringes sold at any drug store make very good bulbs for this work. It is only necessary to cut off a small portion of the nozzle of the ear syringe. The thicker-walled rubber bulbs made for Koch syringes respond more quickly and are more durable. The illustrations show the rubber bulbs attached directly to the mouth-pieces of the pipettes. We have found it more convenient to bring the bulb by means of glass and rubber tubing to the base of the retort stand.

I have used pipettes in accordance with these two methods during the past twelve months in work with toxines and antitoxins, and have concluded that they are quicker, more accurate, and more satisfactory than the old freehand technique.<sup>a</sup>

In working out the problems connected with the accurate methods of measuring given volumes of toxine and antitoxin, I have had the help of the Bureau of Standards, and am indebted especially to Dr. L. A. Fischer and Mr. N. S. Osborne, of the Bureau, for many useful suggestions.

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<sup>a</sup> This method was demonstrated at a meeting of the Society of American Bacteriologists, Philadelphia, December 27, 1904.

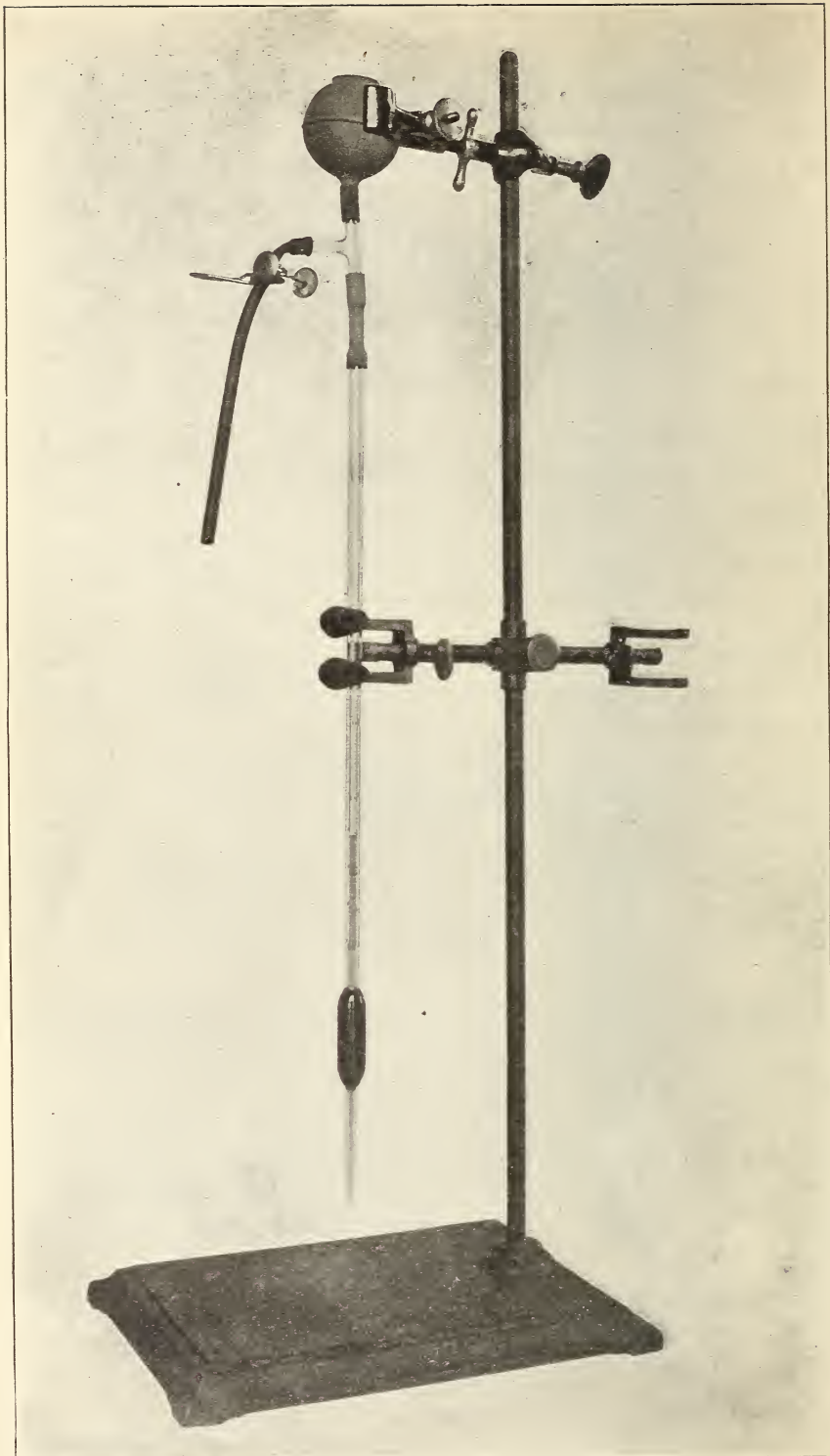


FIG. 13.—Method of using delivery pipettes.

## METHOD OF INOCULATING THE ANIMALS.

The method used for inoculating the animals has been described in Bulletin No. 19 of the Hygienic Laboratory, Public Health and Marine-Hospital Service, entitled "A method for inoculating animals with precise amounts." and only the essential features as applicable to this work will be repeated.

The syringe used for carrying out this technique is a modification of the old Koch syringe.

The needles are sterilized separately by the usual method of boiling in a 1 per cent sodium carbonate solution.

The needle is then screwed on the barrel of the syringe and the joint tested by drawing some sterile salt solution in and out several times. If the joint is tight and the needle pervious, the outside is dried with a little piece of sterile gauze and the needle is now plunged into a jar of sterilized albolene. The albolene acts as a temporary plug, preventing any of the fluid that is placed in the syringe from escaping until it is injected into the animal.

The necessary number of syringes are prepared, one for each animal. In testing diphtheria toxine and antitoxin we sometimes have a battery of fifty or sixty thus prepared, arranged on the rack as shown in the accompanying diagram (fig. 15).

The amount of fluid desired to inject into the animal is now carefully measured directly into the barrel of the syringe. This is injected into the animal and then, without withdrawing the needle, the bulb is removed. The necessary quantity of salt solution is quickly run into the barrel, washing down the sides, and this in turn is injected into the animal.

When the syringes contain fluid they can not be inverted, as is the case with a piston syringe. It is not necessary, how-

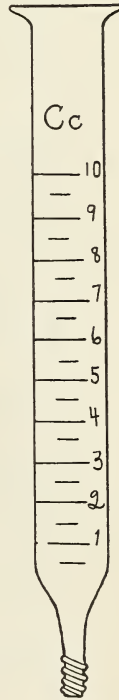
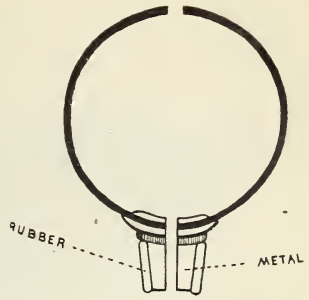


FIG. 14.—Showing the three parts of the syringe, viz, the rubber bulb, the glass barrel and the needle.

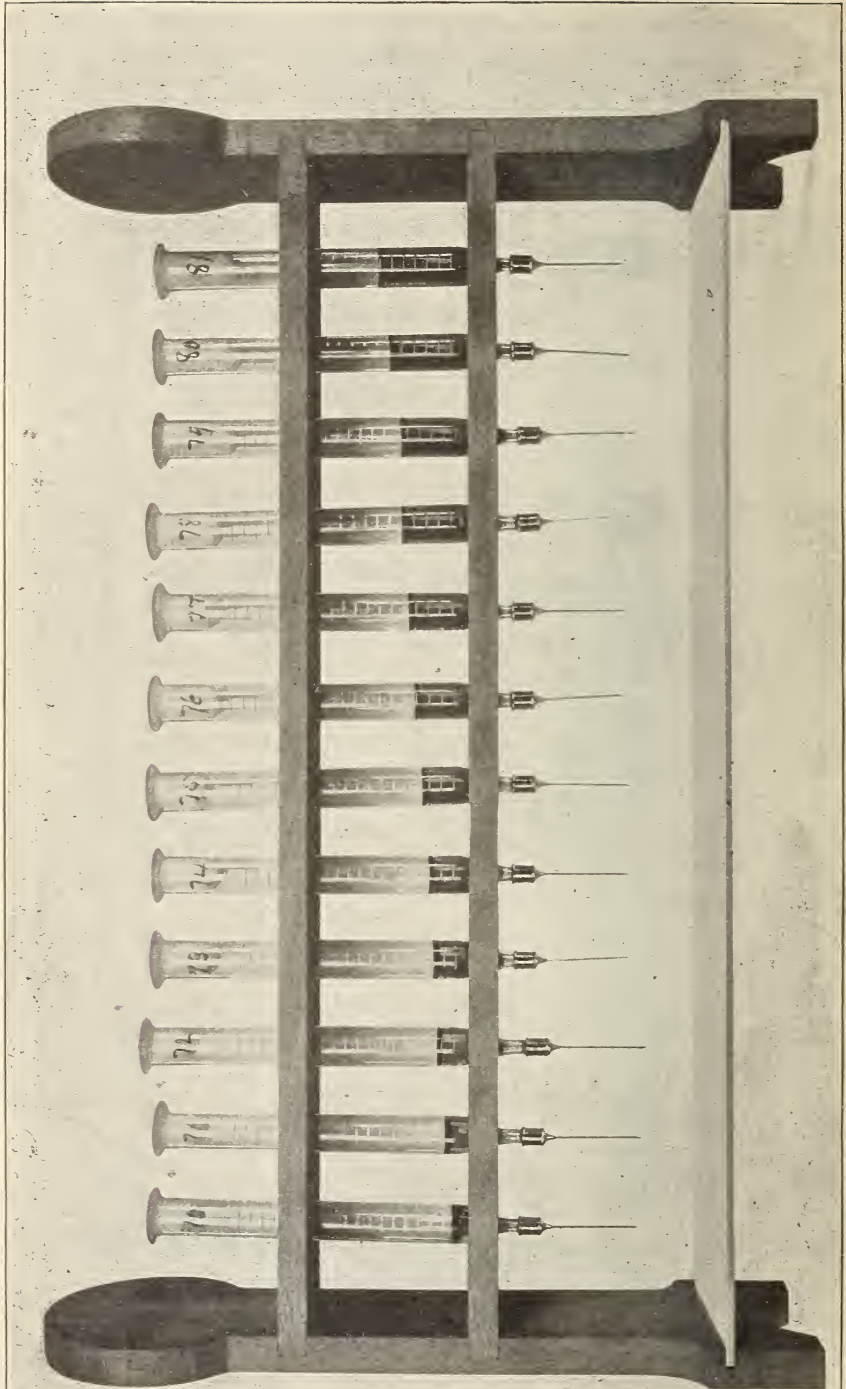


FIG. 15.—A battery of 12 syringe barrels ready for use. The bottom shelf is of milk-white ground glass to show a leak and is used to write upon.



ever, to hold them upright, as might at first be supposed. They may be tilted to a greater angle than  $45^{\circ}$  without danger of the fluid running out.

Each glass barrel is numbered with the number of the experiment or of the animal to receive the injection. This is convenient and avoids confusion.

The syringes are prepared and filled in a special room where the exact measuring is done, and the rack is then found handy to carry the syringes to the animal room where the work of injection is carried on.

In using this method in standardizing diphtheria antitoxin it is very important to shake and roll the syringe very actively so as to obtain an intimate mixture of the toxine with the serum.

The toxine is first measured into the syringe barrel, then the diluted serum. The two are thoroughly mixed by agitating the syringe and the mixture allowed to stand at room temperature in diffused light one hour before it is inoculated into the guinea pig.

The dilutions are so arranged that the guinea pig always receives a total of  $\frac{1}{2}$  c. c. of fluid, thereby insuring constant pressure effects.

We always dilute our serums so that the amount of antitoxin desired will be contained in just 1 c. c. of the dilution. It is preferable to dilute the toxins so that the amount of desired poison will be contained in 2 c. c. or less of solution. In this way we have at least 1 c. c. left to make up the total of  $\frac{1}{2}$  c. c. with which to wash out the syringe barrel.

#### THE GUINEA PIG.

In this work much depends upon the guinea pig. Animals sometimes show such marked idiosyncracies in their reaction to certain poisons that it is remarkable in case of diphtheria toxine that a guinea pig should show comparatively little of this individuality. It may be stated in general terms that the guinea pig as a vital factor in the standardization of diphtheria antitoxin is quite as dependable as our ordinary weights and measures.

It is of course necessary to use pigs under standard or normal conditions, of a definite weight, and approximately the same age. They should be bred from reliable stock, and fed and caged so as to insure vigorous animals.

In order to meet all the exacting requirements we raise our own guinea pigs, thus insuring animals of reliable and constant conditions. Our pigs are fed upon oats and green food such as cabbage, carrots, and grass in season.

Theobald Smith<sup>a</sup> has recently shown that some female guinea pigs give birth to progeny all of which seem to show a marked resistance

<sup>a</sup> Smith, Theobald: Degrees of susceptibility to diphtheria toxin among guinea pigs. Transmission from parent to offspring. Jour. med. res., v. 13 (3), p. 341.

to the diphtheria toxine. Such hereditary influences, which would seriously affect the results, should be guarded against by elimination of this stock.

*Weight of the guinea pig.*—Ehrlich prescribes the use of guinea pigs weighing 250 grams. We consider a pig weighing anywhere from 250 to 280 grams as complying with this requirement.

The weight of a young guinea pig varies with the quantity of food and water taken and the activity of metabolism. We have found young hungry pigs to eat as much as 35 grams in a day. The weight of a young pig will ordinarily change from 10 to 20 grams in a day, depending upon the food and water taken. We, therefore, always weigh our guinea pigs in the morning before feeding time. We sometimes use guinea pigs weighing more than 280 grams, but less than 350 grams, for our first work on a toxine or serum to determine its approximate strength.

In our experience a guinea pig weighs about 100 grams at birth, and is between six and eight weeks old before it weighs the required 250 grams. Occasionally, when the mother gives birth to only one, we have found, under such favorable conditions, that this single offspring may gain so rapidly as to weigh 250 grams before it is four weeks old.

We do not always have enough guinea pigs of our own raising to carry on the work. In that case we buy from reliable dealers, insisting on pigs weighing less than 225 grams, so that we never use a pig that has not been in the laboratory under observation ten days or two weeks.

The pigs are weighed upon a spring-balance scales. These scales are sufficiently accurate, weighing to 2.5 grams, and are much quicker and more convenient than pan balances with weights.

As soon as the young pigs are old enough to be weaned they are divided, separating the males from the females. Pregnant female pigs should not be used in this work.

A pig having been selected and weighed has a card made for it with a rough diagram, on which is indicated its peculiarities of color or other marks. This is a satisfactory method of identifying the animal. The character of card is here shown (fig. 16).

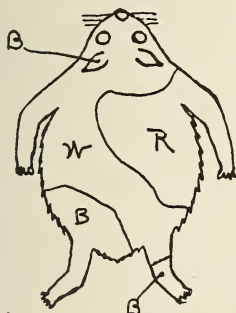
*Technique of operation.*—The abdomen is shaved the day before operation, clearing the site of operation so that we may readily see just what we are doing. An area about 2 inches in diameter is shaved.

The preparation of the animal card shown in fig. 16, the shaving, etc., is done the day before the operation, so that the pig is not handled more than necessary to receive the injection on the day of the operation.

The pig is held by an assistant and the needle introduced in the left flank from one-half to an inch above the supraspinous process of the

TREASURY DEPARTMENT,  
PUBLIC HEALTH AND MARINE-HOSPITAL SERVICE,  
HYGIENIC LABORATORY — Form No. 8987.

## ANIMAL RECORD CARD.



Subject *Diphtheria L+*

Weight *250* No. *1567*

Operator *myr*

Marks *♀*

*Own raising*

Date *1-25, 1905, 3 p.m.*

† Date *1-29, 1905, 5 p.m.*

*.22 cc Tox. #7 + 1 cc Ehrlich 15. II. 05*

*Autopsy 1:30:05. 10 a.m.*

*Severe local reaction, hemorrhagic.*  
*- Skin bound down by plastic*  
*exudate. Edema marked, ex-*  
*tending to neck.*

*No fluid in pleuras.*

*Peritoneum normal.*

*Adrenals injected and swollen.*

*Ex.*

ileum. The needle is introduced its whole length (1.25 inch) strictly subcutaneously toward the middle line. This part of the operation is arranged so that the point of the needle will be just about at the linea alba.

It is of the greatest importance to keep the needle out of the peritoneal cavity, and care must also be exercised not to pierce the skin too superficially, and it is essential to keep out of the muscles.

Probably no part of the entire procedure is more important than the inoculation of the toxine and antitoxin into the proper tissue of the guinea pig. By always injecting the toxine into the same tissues we insure three factors: (1) The rate of absorption, (2) the pressure effects are relatively the same in the same anatomical structures, and (3) the relation between the toxine and the receptors of the cells and body juices is comparatively constant when the injection is made into the same anatomical structures. If any of the toxine enters the peritoneal cavity the rapid absorption may result in the untimely death of the pig with an extensive hemorrhagic reaction.

Still greater care must be exercised to keep the toxine out of the muscles. This point was brought out by Ehrlich and has since been emphasized by S. J. Meltzer<sup>a</sup> and John Auer in their work "On the rate of absorption from intramuscular tissue," with curare and adrenalin.

It has been shown that the rate of absorption from muscular tissue is so active that poisons injected into the muscles are apparently two and three times as strong as when injected into the subcutaneous tissue.

Ehrlich selects for the site of injection the skin at the median line in the region of the xiphoid process of the sternum, and is careful to insert the needle purely subcutaneously by pinching up the skin which is loose in this region.

For the purposes of determining at autopsy the exact site at which the toxine and antitoxin mixtures have been inoculated, little particles of burnt cork are used by Ehrlich. In this laboratory we use a little sterilized powdered animal charcoal, simply for its convenience. Upon dissection the particles of carbon may plainly be seen and show the place where the fluid was injected. This technique has its particular value in determining the  $L^0$  dose.

We have found that if the fluid enters the proper abdominal layer it produces an egg-shaped swelling parallel to and overlying the linea alba.

As soon as the toxine-antitoxin mixture is injected into the animal the rubber bulb is removed and an assistant adds the necessary amount of salt solution to make up the 4 c. c. which, after washing down the

<sup>a</sup> Meltzer & Auer: On the rate of absorption from intramuscular tissue. *Am. med.* (abstract), v. 9 (102), Jan. 14, 1905, p. 75.



sides of the syringe, is in turn forced under the skin. Care to avoid the injection of an unnecessary amount of air should be taken.

The inoculation should be done rapidly and without unnecessary violence, which may affect the results. A trained assistant will hold the guinea pig, without causing struggling, and an experienced operator will cause little pain other than the prick of the needle through the skin.

Care must of course be taken in inoculation that none of the fluid escapes. We do not attempt to disinfect the skin.

*Effect upon the guinea pig.*—After inoculation the guinea pigs are kept two in a cage and not disturbed until the seventh day. Keeping many animals together in a pen may give irregular results, because the strong and lusty pigs worry the sick ones and may hasten their end. Examining the pigs too often or too roughly must also be avoided. Theobald Smith believes that palpating the edema, caused by the reaction of the toxine at the site of inoculation, may cause the poison to break beyond the confines nature is setting up as a barrier, and may thus hasten the result. We have found that there is little to be learned in weighing or examining pigs during the first week, and we therefore leave them undisturbed during this time. They are weighed on the seventh day and each week following until the fourth week, when, if gaining weight and in good condition, they are passed from observation.

Guinea pigs that show late effects of *toxone*, as indicated by paralysis, will do so some time after the fourteenth day and before the thirtieth day with great regularity. The facts of paralysis, sloughs, ulcers, etc., are carefully noted on the records.

When an animal dies an autopsy is always made in order to insure that the lesions are typical, and to guard against the possibility of infections—pneumonia, tuberculosis, pseudotuberculosis, etc., and to insure the fact that the toxine was not injected into the muscles or the peritoneum—which may have rendered the animals more susceptible.

The guinea pig shows a remarkable constancy in its reaction to varying amounts of the diphtheria poison. Overpowering doses of the toxine—say,  $100 \times \text{MLD}$ —almost invariably kill the animals in about twenty-four hours. It is with the rarest exception that a guinea pig will die as a result of the diphtheria poison in less than twenty hours. Smaller amounts cause the death of the animal in from thirty-six to forty-eight hours. As we approach the limit of the minimal lethal dose, or the mixture containing the  $L+$  dose of the toxine and one immunity unit, we find one of three results:

- (1) The animal dies from acute poisoning on about the fourth day.
- (2) The animal develops post-diphtheritic paralysis between the fourteenth and thirtieth days.
- (3) Recovery.

The first result, viz. the acute death of the guinea pig, is of special interest to us, because it is the factor which determines the strength of the toxine and antitoxin.

Guinea pigs dying acutely do so with great regularity on the fourth day, the actual time averaging about three days twelve hours. Occasionally guinea pigs will die between two and a half and three and a half days as a result of the injection of a minimal lethal dose or as the result of an injection of the mixture of toxine and antitoxin containing the L+ dose of the former and one immunity unit of the latter. In these cases the autopsy will often show a reason for this lack of resistance indicated by the severity of the reaction and especially the presence of pleuritic exudates, or the guinea pig may have pneumonia or some other disease. Occasionally more resistant animals will die on the fifth day, rarely on the sixth day, and very exceptionally on the seventh, eighth, or ninth days.

If the poison is not sufficient to kill the animal acutely as above described, paralysis may supervene. The symptoms of paralysis do not appear before the fourteenth day and usually show themselves in the legs. The hind legs are commonly affected first. The guinea pig not unusually recovers after marked paralytic symptoms, but ordinarily the fore legs become limp and useless, respiration indicating phrenic involvement makes its appearance, and death supervenes.

## EXAMINATION OF SERUMS MADE BY LICENSED MANUFACTURERS.

The act of Congress approved July 1, 1902, entitled "An act to regulate the sale of viruses, serums, toxins, and analogous products in the District of Columbia, to regulate interstate commerce in said articles, and for other purposes," and the regulations framed thereunder, approved February 21, 1903, imposed upon the Director of the Hygienic Laboratory the duty of examining vaccines and antitoxins for purity and potency.

Accordingly purchases are made for the Hygienic Laboratory from time to time on the open market by officers of the Public Health and Marine-Hospital Service stationed in various parts of the country. The antitoxin is always bought from reliable druggists who keep the product under proper conditions of light, temperature, etc. Several grades of diphtheria antitoxin made by each licensed manufacturer are bought and sent to the Hygienic Laboratory by mail for the purposes of these tests.

The serums are tested not only for potency, but also to determine their freedom from contamination by foreign bacteria, and finally to insure the absence of chemical poisons, especially tetanus toxin. Note is made of the physical appearance of the serum, and tests are made to determine whether an excessive amount of preservative has been added.

A careful memorandum is made of the facts given by the manufacturer, as stated upon the label, as to the number of units contained in the package, and the date beyond which the contents can not be expected beyond a reasonable doubt to yield a specific result. Note is also made of the manufacturer's compliance with the law requiring that the product be plainly marked with the name of the article, and the name, address, and license number of the manufacturer.

Delinquencies that occasionally come to light in these examinations are at once reported to the Surgeon-General, U. S. Public Health and Marine-Hospital Service, who takes the necessary steps requiring the immediate withdrawal of the particular lot of serum from the market and institutes measures to prevent a repetition of similar errors.

In examining the unit strength of antitoxin sold by licensed manufacturers the first step is to measure carefully the quantity of fluid contained in the syringe, bottle, or special container, whatever it may be. For this purpose the serum is emptied into a cylinder that has

been standardized by the Bureau of Standards in which the total amount of the serum may be accurately read to the fractional part of a cubic centimeter.

From 0.5 to 1 c. c. of each lot of serum is planted into a large amount of bouillon in order to dilute the preservative. This is incubated at body temperature and any growth that may appear is determined by the usual bacteriological methods.

The number of units that the serum contains is then estimated by the following procedure:

If a syringe contains 4 c. c. of serum and is labeled 1,000 units it must of course have at least 250 units to each cubic centimeter. We would then test such a sample upon four or five guinea pigs to see whether its unit strength is above or below the value claimed for it. If the strength of the serum is 10 per cent below that claimed, a special report is made to the Surgeon-General to this effect, the manufacturer is notified that all the serum bearing this laboratory number must be withdrawn from the market, and the matter is investigated.

The tests to determine the strength of commercial serums sold upon the open market are made against a toxine that has been very carefully tested to determine its exact L+ dose. Controls at the same time are always made against both Ehrlich's normal serum and the official standard serum made in this laboratory. In case of doubt or contradictory results the work is always repeated, making the second tests against the L+ doses of two toxines.

As weak serums are of doubtful therapeutic value, we do not favor the sale of diphtheria antitoxic serum containing less than 250 units per c. c. If a serum bought on the market contains less than 200 units per c. c., the fact is reported to the Surgeon-General, who requests its withdrawal from sale and a discontinuance of the practice.

To determine that an excessive amount of preservative belonging to the phenol group has not been added, the following tests, modified from similar tests suggested by Ehrlich, are employed:

It has been found that 0.5 c. c. of a 0.5 per cent solution of phenol will kill a medium-sized mouse if injected subcutaneously. The quantity of phenol contained in 0.5 c. c. of such a solution represents 0.0025 gram. It requires 1 c. c. of a 0.5 per cent solution of tricresol to produce the same result. One c. c. of a 0.5 per cent solution contains 0.005 c. c. of tricresol. The above facts have been experimentally confirmed in this laboratory.

As phenol is not used as a preservative in this country for diphtheria antitoxic serums, preference being given by manufacturers to tricresol, we inoculate mice subcutaneously with 1 c. c. of their serum. Mice so inoculated sometimes show trembling and other manifestations of tricresol poisoning, which shows that the serums contain very



Potency test for Blank's Diph. antitoxin # 64 - B 721 opus 6

Date labeled Return after Sept. 10-1905.

Date tested 11-2-04

Character of package Syringe

Amount of contents 4 cc.

No. of units labeled 1,000

= 250 units per cc.

Purchased by F.I. at W.A.W. in Phila. Pa. Oct. 15 1904

Physical appearance Opalescent

Odor of tricresol

0.5 cc planted in 100 cc. bouillon: result = Sterile

1.0 cc subcutaneously into mouse: = No effect

1.5 cc intraperitoneally into guinea pig: = No effect

Tested 10-2-04 for 200 units per cc G.P. no. 642 Result - nil



"	"	225	"	"	"	643	"	"
"	"	250	"	"	"	644	"	"
"	"	300	"	"	"	645	"	Tested 3 days 16 hrs

Fig. 17.—Illustrating record used for testing the potency and purity of diphtheria antitoxin bought on the open market.

nearly this percentage of tricresol. As the serums practically never contain an excess of preservatives, these inoculations into mice serve as a further test for tetanus and other poisons.

Finally, all that is left of the serum is injected into the peritoneum of a guinea pig in order to discover the presence of any virulent substance of a bacterial or toxic nature.

These tests are repeated with sufficient frequency to establish the fact that the serums made by each licensed manufacturer sold upon the market are pure and potent.

Tables found very useful for diluting the serum in making these tests follow:

TABLE FOR DILUTING SERUMS 100 TO 500 UNITS PER CUBIC CENTIMETER.

*First dilution.*

$$1+9=1:10 \quad 1 \text{ c. c. } = 0.1$$

*Second dilution.*

1 of 1st dil.—

+ 9=1:100	1 c. c. = 0.01	or $\frac{1}{100}$	= 100 units per c. c.
+10=1:110	1 c. c. = 0.00999	or $\frac{1}{110}$	= 110 units per c. c.
+11=1:120	1 c. c. = 0.00833	or $\frac{1}{120}$	= 120 units per c. c.
+12=1:130	1 c. c. = 0.00769	or $\frac{1}{130}$	= 130 units per c. c.
+13=1:140	1 c. c. = 0.00714	or $\frac{1}{140}$	= 140 units per c. c.
+14=1:150	1 c. c. = 0.00666	or $\frac{1}{150}$	= 150 units per c. c.
+15=1:160	1 c. c. = 0.00625	or $\frac{1}{160}$	= 160 units per c. c.
+16=1:170	1 c. c. = 0.00588	or $\frac{1}{170}$	= 170 units per c. c.
+17=1:180	1 c. c. = 0.00555	or $\frac{1}{180}$	= 180 units per c. c.
+18=1:190	1 c. c. = 0.00526	or $\frac{1}{190}$	= 190 units per c. c.
+19=1:200	1 c. c. = 0.005	or $\frac{1}{200}$	= 200 units per c. c.
+20=1:210	1 c. c. = 0.00476	or $\frac{1}{210}$	= 210 units per c. c.
+21=1:220	1 c. c. = 0.00454	or $\frac{1}{220}$	= 220 units per c. c.
+22=1:230	1 c. c. = 0.00434	or $\frac{1}{230}$	= 230 units per c. c.
+23=1:240	1 c. c. = 0.00416	or $\frac{1}{240}$	= 240 units per c. c.
+24=1:250	1 c. c. = 0.004	or $\frac{1}{250}$	= 250 units per c. c.
+25=1:260	1 c. c. = 0.00384	or $\frac{1}{260}$	= 260 units per c. c.
+26=1:270	1 c. c. = 0.0037	or $\frac{1}{270}$	= 270 units per c. c.
+27=1:280	1 c. c. = 0.00357	or $\frac{1}{280}$	= 280 units per c. c.
+28=1:290	1 c. c. = 0.00345	or $\frac{1}{290}$	= 290 units per c. c.

TABLE FOR DILUTING SERUMS 100 TO 500 UNITS PER CUBIC CENTIMETER—Continued.

*Second dilution*—Continued.

1 of 1st dil.—

+29=1:300	1 c. c.=0.00333 or $\frac{1}{300}$ =	300 units per c. c.
+30=1:310	1 c. c.=0.00322 or $\frac{1}{310}$ =	310 units per c. c.
+31=1:320	1 c. c.=0.00312 or $\frac{1}{320}$ =	320 units per c. c.
+32=1:330	1 c. c.=0.00303 or $\frac{1}{330}$ =	330 units per c. c.
+33=1:340	1 c. c.=0.00294 or $\frac{1}{340}$ =	340 units per c. c.
+34=1:350	1 c. c.=0.00285 or $\frac{1}{350}$ =	350 units per c. c.
+35=1:360	1 c. c.=0.00277 or $\frac{1}{360}$ =	360 units per c. c.
+36=1:370	1 c. c.=0.0027 or $\frac{1}{370}$ =	370 units per c. c.
+37=1:380	1 c. c.=0.00263 or $\frac{1}{380}$ =	380 units per c. c.
+38=1:390	1 c. c.=0.00256 or $\frac{1}{390}$ =	390 units per c. c.
+39=1:400	1 c. c.=0.0025 or $\frac{1}{400}$ =	400 units per c. c.
+40=1:410	1 c. c.=0.00244 or $\frac{1}{410}$ =	410 units per c. c.
+41=1:420	1 c. c.=0.00238 or $\frac{1}{420}$ =	420 units per c. c.
+42=1:430	1 c. c.=0.00232 or $\frac{1}{430}$ =	430 units per c. c.
+43=1:440	1 c. c.=0.00227 or $\frac{1}{440}$ =	440 units per c. c.
+44=1:450	1 c. c.=0.00222 or $\frac{1}{450}$ =	450 units per c. c.
+45=1:460	1 c. c.=0.00217 or $\frac{1}{460}$ =	460 units per c. c.
+46=1:470	1 c. c.=0.00213 or $\frac{1}{470}$ =	470 units per c. c.
+47=1:480	1 c. c.=0.00208 or $\frac{1}{480}$ =	480 units per c. c.
+48=1:490	1 c. c.=0.00204 or $\frac{1}{490}$ =	490 units per c. c.
+49=1:500	1 c. c.=0.002 or $\frac{1}{500}$ =	500 units per c. c.

TABLE FOR DILUTING SERUMS 200 TO 1,000 UNITS PER CUBIC CENTIMETER.

*First dilution.*

$$1+19=1:20 \quad 1 \text{ c. c.} = 0.05.$$

*Second dilution.*

1 of 1st dil.—

+ 9=1:200	1 c. c.=0.005 or $\frac{1}{200}$ =	200 units per c. c.
+10=1:220	1 c. c.=0.00454 or $\frac{1}{220}$ =	220 units per c. c.
+11=1:240	1 c. c.=0.00416 or $\frac{1}{240}$ =	240 units per c. c.
+12=1:260	1 c. c.=0.00384 or $\frac{1}{260}$ =	260 units per c. c.
+13=1:280	1 c. c.=0.00357 or $\frac{1}{280}$ =	280 units per c. c.

TABLE FOR DILUTING SERUMS 200 TO 1,000 UNITS PER CUBIC CENTIMETER—Continued.

Second dilution—Continued.

1 of 1st dil.—

+14=1:300	1 c. c.=0.00333 or $\frac{1}{300}$	= 300 units per c. c.
+15=1:320	1 c. c.=0.00312 or $\frac{1}{320}$	= 320 units per c. c.
+16=1:340	1 c. c.=0.00294 or $\frac{1}{340}$	= 340 units per c. c.
+17=1:360	1 c. c.=0.00277 or $\frac{1}{360}$	= 360 units per c. c.
+18=1:380	1 c. c.=0.00263 or $\frac{1}{380}$	= 380 units per c. c.
+19=1:400	1 c. c.=0.0025 or $\frac{1}{400}$	= 400 units per c. c.
+20=1:420	1 c. c.=0.00238 or $\frac{1}{420}$	= 420 units per c. c.
+21=1:440	1 c. c.=0.00227 or $\frac{1}{440}$	= 440 units per c. c.
+22=1:460	1 c. c.=0.00217 or $\frac{1}{460}$	= 460 units per c. c.
+23=1:480	1 c. c.=0.00208 or $\frac{1}{480}$	= 480 units per c. c.
+24=1:500	1 c. c.=0.002 or $\frac{1}{500}$	= 500 units per c. c.
+25=1:520	1 c. c.=0.00192 or $\frac{1}{520}$	= 520 units per c. c.
+26=1:540	1 c. c.=0.00185 or $\frac{1}{540}$	= 540 units per c. c.
+27=1:560	1 c. c.=0.00182 or $\frac{1}{560}$	= 560 units per c. c.
+28=1:580	1 c. c.=0.00172 or $\frac{1}{580}$	= 580 units per c. c.
+29=1:600	1 c. c.=0.00166 or $\frac{1}{600}$	= 600 units per c. c.
+30=1:620	1 c. c.=0.00161 or $\frac{1}{620}$	= 620 units per c. c.
+31=1:640	1 c. c.=0.00156 or $\frac{1}{640}$	= 640 units per c. c.
+32=1:660	1 c. c.=0.00151 or $\frac{1}{660}$	= 660 units per c. c.
+33=1:680	1 c. c.=0.00147 or $\frac{1}{680}$	= 680 units per c. c.
+34=1:700	1 c. c.=0.00143 or $\frac{1}{700}$	= 700 units per c. c.
+35=1:720	1 c. c.=0.00139 or $\frac{1}{720}$	= 720 units per c. c.
+36=1:740	1 c. c.=0.00135 or $\frac{1}{740}$	= 740 units per c. c.
+37=1:760	1 c. c.=0.00131 or $\frac{1}{760}$	= 760 units per c. c.
+38=1:780	1 c. c.=0.00128 or $\frac{1}{780}$	= 780 units per c. c.
+39=1:800	1 c. c.=0.00125 or $\frac{1}{800}$	= 800 units per c. c.
+40=1:820	1 c. c.=0.00122 or $\frac{1}{820}$	= 820 units per c. c.
+41=1:840	1 c. c.=0.00119 or $\frac{1}{840}$	= 840 units per c. c.
+42=1:860	1 c. c.=0.00116 or $\frac{1}{860}$	= 860 units per c. c.
+43=1:880	1 c. c.=0.00113 or $\frac{1}{880}$	= 880 units per c. c.
+44=1:900	1 c. c.=0.00111 or $\frac{1}{900}$	= 900 units per c. c.
+45=1:920	1 c. c.=0.00109 or $\frac{1}{920}$	= 920 units per c. c.
+46=1:940	1 c. c.=0.00106 or $\frac{1}{940}$	= 940 units per c. c.
+47=1:960	1 c. c.=0.00104 or $\frac{1}{960}$	= 960 units per c. c.
+48=1:980	1 c. c.=0.00102 or $\frac{1}{980}$	= 980 units per c. c.
+49=1:1,000	1 c. c.=0.001 or $\frac{1}{1000}$	= 1,000 units per c. c.



## SERUM ANTIDIPHThERICUM IN THE PHARMACOPŒIA.

The next edition of the United States Pharmacopœia, being the eighth decennial revision, 1900, which is to appear shortly, will contain an antitoxic serum for the first time. The serum will be known officially as antidiphtheric serum or *Serum antidiphthericum* and the unit will be recognized as that approved or established by the United States Public Health and Marine-Hospital Service.

The official text, which has been kindly furnished by Professor Remington in advance, will be as follows:

### SERUM ANTIDIPHThERICUM

#### ANTIDIPHThERIC SERUM

#### DIPHThERIA ANTITOXIN

A fluid separated from the coagulated blood of a horse *Equus caballus* Linné, immunized through the inoculation of diphtheric toxin. It should be kept in sealed glass containers, in a dark place, at temperatures between 4.5° and 15° C. (40° and 59° F.).

A yellowish or yellowish-brown, transparent or slightly turbid liquid, odorless or having a slight odor, due to the presence of the antiseptic used as a preservative.

Specific gravity: 1.025 to 1.040 at 25° C. (77° F.).

Antidiphtheric Serum gradually loses its power, the loss in one year varying between 10 per cent. and 30 per cent. Each container should be furnished with a label or statement, giving the strength of the Antidiphtheric Serum, expressed in antitoxic units, the name and percentage by volume of the antiseptic used for the preservation of the liquid (if such be used), the date when the Antidiphtheric Serum was last tested, and the date beyond which it will not have the strength indicated on the label or statement.

The standard of strength, expressed in units of antitoxic power, should be that approved or established by the United States Public Health and Marine-Hospital Service.

*Average dose.*—3000 units.

*Immunizing dose for well persons.*—500 units.

The only other pharmacopœia officially recognizing diphtheria antitoxin is the *Arzneibuch für das Deutsche Reich* (Pharmacopœia Germanica), fourth edition, 1900. The following is a translation of the German text:

### SERUM ANTIDIPHThERICUM—DIPHThERIE-HEILSERUM.

The blood serum of horses which have been immunized against the diphtheria poison. It is allowed to be sold in commerce by author-

ized manufacturers only after it has been tested by the Königlich preussische Institut für experimentelle Therapie zu Frankfurt a. M. These tests include the strength of the serum in immunity units (Immunisirungseinheiten=I. E.), the freedom from bacteria, and the percentages of substances (phenol or trikresol), which have been added as preservatives.

It is offered for sale in both the liquid and solid forms.

Liquid and solid antidiphtheric serum are purveyed only in bottles which are officially sealed. Upon the label is stated the place of manufacture, the antitoxic value of one cubic centimeter, and the total contents of the bottle; also the control number and the date on which the official control was exercised. These bottles are placed in light-proof packages containing the same label; the lead seals show an eagle or a lion on the obverse and the total number of immunity units (I. E.) contained in the bottle on the reverse.

The liquid antidiphtheric serum is a yellow, clear fluid having at most a very slight precipitate: it has the odor of the preservative used. It is put up in bottles of various form and color, the contents of which contain from 100 to 3,000 I. E. The bottles most frequently used are those containing:

- No. 0= 200 I. E.
- No. I= 600 I. E. (or 500 I. E.)
- No. II=1,000 I. E.
- No. III=1,500 I. E.

Antidiphtheric serum which contains more than 300 I. E. in 1 c. c. is considered a high grade serum.

The solid antidiphtheric serum is a dried serum of high grade, and contains at least 5,000 I. E. in 1 gram. It contains no antiseptic or other added substance. It appears as a yellowish-white powder, soluble in ten parts of water, giving a solution which, in color and appearance, resembles the corresponding liquid antidiphtheric serum.

Single doses of from 250 to 1,000 I. E., and containing 2 to 6 c. c., are placed in white glass-stoppered bottles. The solution should be made with sterile water in the original bottle, using 1 c. c. for each 250 I. E., and should be prepared fresh each time. The solution should be clear except for little albuminous particles, and should be used from the original bottle.

Serum with a marked permanent cloudiness or an abundant precipitate is not allowed to be dispensed by the apothecaries; also serums with certain control numbers which have been recalled.

TO BE KEPT IN A COOL PLACE AND PROTECTED FROM THE LIGHT.

## THE OFFICIAL METHODS USED IN GERMANY FOR TESTING DIPHThERIA TOXINE AND ANTITOXIN.

The German methods which follow have been taken largely from E. Marx: *Die Experimentelle Diagnostik Serumtherapie und Prophylaxe der Infectionskrankheiten*, 1902.

In Germany the governmental control of diphtheritic serum is effected through the imperial act of December 31, 1894, which forbids unrestricted commerce in diphtheritic serum. The sale and traffic in diphtheritic serum is controlled by the *Königliches Institut für experimentelle Therapie zu Frankfurt a. M.*, which is designated as the official place of examination for the Empire. Apothecaries are allowed to deal only in sera which are thus controlled.

This control naturally begins at the place of manufacture and consists of an inspection to assure the use of none but healthy horses in the production of serum. Official regulations are prescribed concerning the animals, the injection of toxines, and the drawing of blood from horses.

When a manufacturer has several liters (3 to 10) of tested serum this quantity is brought to the Government officer (known as the *Abnahmebeamte*) at the place of its manufacture. At the same time exact data upon the history of the particular serum must be given. The *Abnahmebeamte* takes a small quantity of the serum, places 3 to 5 c. c. in each of six or eight bottles, which he guards with a lead seal, and, attaching the necessary labels, sends the bottles to the testing station at Frankfurt a. M. The serum that remains at the factory is placed by the *Abnahmebeamte* under official lock and key until he receives the results of the tests.

The official testing of diphtheria antitoxin was started in Germany at the *Institut für Infectionskrankheiten*, of Berlin, February 20, 1895.<sup>a</sup>

A serum is tested—

(a) To see that it is harmless, and

(b) For its antitoxic value.

1. It must be clear or, at most, have a very slight precipitate.
2. It must be free from bacteria, as tested by bacteriological methods.
3. It must not contain more than 0.5 per cent of carbolic acid or cresol.

<sup>a</sup>Ehrlich: *Die staatliche controle des diphtherieserums*. *Ber. klin. woch.*, v. 33 (20), May 18, 1896, pp. 441-443.

The institute for testing the serum does not determine in its official tests the exact antitoxic value of sera sent it, but determines by means of the L+ dose of the test poison whether the serum contains at least the value claimed for it by the manufacturer. The testing for the sterility of the sera is done in accordance with well known bacteriologic rules, by making aërobic and anaërobic agar and bouillon cultures.

In order to determine the amount of disinfectants added to the serum white mice are used. They are inoculated subcutaneously with 0.5 c. c. of the serum. Solutions of carbolic acid containing more than 0.5 per cent unerringly cause, in this amount, the death of the animal. Finally, guinea pigs are inoculated with 10 c. c. of the serum, and they must remain well.

If the serum has complied with all the official tests, it is considered reliable, and, after due notification of the fact, it is immediately bottled in the presence of the local official. It is the duty of this officer to seal each bottle with his lead seal. His control is a guaranty of the procedure of this part of the process, and he is responsible for the proper labeling of the bottles that are sold on the market.

A further control is carried out in this way: Of every test number in the testing institute six and twenty-four months afterwards the serum is again tested to determine whether it contains the stated value and has not lost strength. Also, a number of hospitals are commissioned, from time to time, as they use the bottles of serum, to test them for sterility. Sera that lose strength or show bacterial contamination are withdrawn from the market.

From experience gained in his work, Ehrlich suggested the following amendments to the instructions for the testing of diphtheria antitoxin, which were officially promulgated by the minister of education, etc., on March 29, 1897:

1. A powdered serum protected against moisture and oxygen serves as the measure by which the strengths of other serums are determined. This powdered serum is preserved in exactly weighed quantities in special vacuum tubes. At this time in the Institut the tubes contain 2 grams each of the dry powdered antitoxin, which have the value of 1,700 times normal strength (1,700 facher Stärke).

2. The serum is dissolved in a mixture of equal parts of a 10 per cent solution of sodium chlorid and glycerin, this mixture favoring the stability of the antitoxin. Every three months a tube is opened and a new solution made. At present the contents of the tubes preserved in the Institut are dissolved in 200 c. c. of the above-mentioned mixture, which gives a test serum containing 17 units in each cubic centimeter.

3. The present test dose of toxin is determined by means of an



immunity unit which is contained in 1 c. c. of the test serum mentioned in paragraph 2, diluted 17 times. This quantity (1 c. c.) of serum is mixed with increasing amounts of the diphtheria poison, and the mixture inoculated into a series of animals, in order to determine with the greatest possible accuracy the least amount sufficient to cause the death of the animals in the first four days. This quantity of the diphtheria poison is then taken as the quantity to be used for the present test dose. Varying quantities of toxin are again added to the same quantity of serum (viz, 1 unit) in order to determine a second limit, namely, that quantity of diphtheria poison which must be added to the serum in order that the poison will be exactly neutralized as indicated by inoculating the mixture into guinea pigs.

4. The estimation of the strength of a diphtheria antitoxin is accomplished by means of a test dose of the poison (see paragraph 3) in this way: The particular test dose—for example, 0.355 c. c.—which is the present test dose of the toxin determined at the Institut, is added to or mixed with 4 c. c. of a mixture containing one unit of the above-mentioned serum.

As the test dose of the poison is determined against 1 c. c. of a normal serum, or against 4 c. c. of a one-fourth normal serum, consequently in testing a serum of (supposed)  $x$  strength the test dose of poison is added to 4 c. c. of a  $\frac{1}{4x}$  dilution of that serum, or against 4 c. c. of a  $\frac{1}{400}$  dilution of a serum of (supposed) one hundred times normal strength.

5. The mixture obtained is injected subcutaneously into guinea pigs weighing 250 to 280 grams. If the animals tested by two members of the Institut die within the first four days, then that particular serum does not contain the strength claimed for it. If the animals die within the fifth or sixth day, then the serum is exactly on the limits of admissibility, and in order to prevent the necessity of soon recalling the serum from the market it is recommended to the manufacturer to add 5 to 10 per cent. Indurations that appear in the test animals are not taken into consideration in this test.

An autopsy is performed upon animals that die, to determine whether complicating diseases are present, such as tuberculosis, pseudotuberculosis, or pneumonia, which may have rendered the animals more susceptible.

6. Either the liquid or solid poison may be used for testing as long as the two limits defined in paragraph 3 have been properly determined and the difference between the two limits does not exceed  $15 \times \text{MLD}$ . Liquid poisons preserved with toluol must be used only under the following conditions:

(1) If after prolonged examination it is known that the stability of the test dose is constant and (2) when the test dose does not exceed

1 c. c. The observations on the quality of the test dose follow in the succeeding paragraphs.<sup>a</sup>

7. The test poisons are, when liquid, to be examined at least once a month upon culture media for sterility.

8. The test dose of poison is to be redetermined every six weeks by means of the test dose of serum in such a way that both the test dose of the poison and its neutralizing point may be determined anew. If in these redeterminations a considerable weakening of the test dose develops, then the poison must be considered as being in dissolution and should be replaced by a new one.

9. The attention of manufacturers must be brought to the fact that the test poison in small quantities is very apt to decompose; particularly a very short exposure to light will cause an appreciable weakening. It is therefore recommended that they obtain every three weeks a new poison from the Institut.

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<sup>a</sup>According to my observations, to carry out the test with exactness it is not necessary for the test dose to contain a maximum amount of poisonous affinities. From the viewpoint of technique, old weakened poisons preserved with toluol are preferred, because after the weakening has taken place they will preserve their value for years.

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HYGIENIC LABORATORY.—BULLETIN No. 22.

M. J. ROSENAU, *Director.*

MAY, 1905.

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# CHLORIDE OF ZINC

AS A

DEODORANT, ANTISEPTIC, AND GERMICIDE.

BY

T. B. McCLINTIC.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.

1905.

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# CHLORIDE OF ZINC AS A DEODORANT, ANTISEPTIC, AND GERMICIDE.

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By THOMAS B. McCLINTIC,

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

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## INTRODUCTION.

This compound of chlorine with zinc had a reputation as a deodorant and disinfectant for many years.

It was used for this purpose in a more or less empirical manner before we were aware of the existence of micro-organisms or the nature of putrefactive changes and long before it had been suspected that bacteriology would take the important rank in the field of science that it justly holds to-day. At the period when it seems to have had its greatest popularity in sanitary work the rationale of disinfection was very poorly understood. As the existence of germs was unknown at that time, the word "germicide" was not in use and the terms deodorant, antiseptic, and disinfectant were used more or less interchangeably and synonymously. Even to-day this is often the case. A substance may have practically no germicidal properties, but if it has the power to mask or destroy offensive odors arising from matter undergoing decay many persons will class it as a disinfectant.

This error is often productive of unfortunate consequences in handling and disposing of infected material and very much augments the difficulties that beset the sanitarian in the performance of his duties. It is too often observed, aboard ship, for instance, that the master considers his vessel disinfected after using a small quantity of one of the various preparations sold on the market as a disinfectant. The preparation used may or may not have germicidal properties; but, assuming the former condition to be the case, the quantity used is usually so limited that, as a rule, all that is accomplished is a certain amount of deodorization.

Of course there is, to a certain extent, a relation existing between the terms in question, a disinfectant usually being a deodorant, but a deodorant is by no means always a disinfectant or even an antiseptic.

Man naturally has an instinctive repugnance to all offensive exhalations, and from the earliest times has sought to overcome their presence in some way, and it is natural that any substance giving promise in this field should gain more or less popularity.

Not many years ago the inhalation of foul odors was regarded as one of the principal etiological factors concerned in the transmission of some of the infectious diseases, which, may in part account for and have justified the use of chloride of zinc.

There is no doubt that the virtues accredited to chloride of zinc have been acquired largely through what power it may have for removing obnoxious effluvia and not because of its power to destroy micro-organisms.

The literature covering the experimental work that has been done with chloride of zinc for the purpose of ascertaining its antiseptic and germicidal properties is meager, and the results that have been published by different investigators are not always satisfactory and sometimes contradictory.

#### REVIEW OF LITERATURE.

Chloride of zinc as a deodorant and disinfectant was very popular in the British navy<sup>a</sup> about the middle of the last century, some of the naval medical officers strongly recommending its use in the treatment of dysentery and in preventing the spread of cholera. It was found particularly useful in overcoming the disagreeable smells arising from the excretions of patients sick with these diseases.

The deputy inspector of royal naval hospitals in Bermuda published a report in 1854<sup>b</sup> in which he regarded chloride of zinc as a most powerful and instantaneous deodorant, and he, too, used it with great success in overcoming the foul emanations arising from patients lying in the wards in every stage of the worst forms of yellow fever. The waving of flags moistened with the solution and the employment of other means recommended for its use dissipated the foul air and restored freshness.

Concerning chloride of zinc as a disinfectant, the royal scientific deputation of medical officers,<sup>c</sup> 1856, states that there is no doubt and no further research is necessary to show that a solution of zinc chloride will perform very good service in protecting the bilge and preventing

<sup>a</sup> Royal Naval Medical Reports: Extracts from official reports upon the effects of chloride of zinc in deodorizing offensive effluvia from cesspools, sewers, etc., and in decomposing poisonous emanations from the bodies of those affected by contagious diseases. *Med. Times and Gaz.*, London, 1853, n. s. 7, pp. 341-344.

<sup>b</sup> Hilditch, E.: Report on deodorizing and disinfecting properties of the chloride of zinc. *Med. Times and Gaz.*, London, 1854, n. s. 9, p. 106.

<sup>c</sup> Ueber den Chlorzink als Desinfectionsmittel. *Viertelj. f. gericht. und off. Medicin*, Berlin, 1856, pp. 104-107.

bilge water of ships from putrefying, and in improving the smell of water-closets, etc., but that it is not to be preferred to chloride of lime and chlorine in contagious diseases.

In 1875 and 1876 Pettenkofer and Mehlhausen<sup>a</sup> directed a number of trials in the German fleet upon the disinfecting value of zinc chloride. Bilge water of a specific gravity 1017 to 1035, with a slightly alkaline reaction, at a temperature of 20° to 30° C., was treated with a solution of 50 to 60 per cent strength in the proportion of 1:100 of bilge. A grayish flocculent precipitate rapidly settled, leaving a nearly clear yellowish liquid. All odor ceased and the organisms seemed to be killed. At the end of four weeks the mixture showed no signs of change. One part of the solution to 1,000 of bilge caused a decrease in the odor; 2 to 1,000 completely removed sulphuretted hydrogen, much reduced the rancid smell, and preserved the liquid for fourteen days.

The German cholera commission of 1879<sup>b</sup> prescribed zinc chloride for the disinfection of bilge water.

Grace Calvert<sup>a</sup> found that a solution of albumin to which 1 per mille of zinc chloride was added required over forty days before germs developed.

Sternberg<sup>c</sup> in 1881 performed some experiments to ascertain the germicidal value of chloride of zinc. He inoculated three rabbits with 0.5, 1, and 2.5 per cent solutions, respectively, that had been mixed with the blood of a rabbit dead of mouse septicemia (*B. murisepticus*) and allowed the mixture to stand from 20 to 30 minutes before inoculation. The rabbit receiving the 1 per cent solution was the only one to die, the other two recovering.

Koch<sup>d</sup> in 1881 did some experimental work with zinc chloride on account of the reputation it had as a disinfectant. It was considered an efficient disinfectant in the proportion of one part in 1,000.

In his experiments he found that the *Micrococcus prodigiosus* was not injured in the least after two days' exposure in a percentage of 1:1,000. He did not observe any difference in the results of similar experiments with a percentage of 1:100 for the first 16 hours' exposure, but after this time observed that the power to develop when transplanted was somewhat diminished as compared with the controls. The *Micrococcus prodigiosus* was not entirely killed after an exposure of 48 hours in a percentage of 1:100.

The spores of anthrax and subtilis grew quite as vigorously after 48 hours' exposure in this percentage as if they had not been exposed.

<sup>a</sup> Rideal: Disinfection and preservation of food. 1903, p. 152.

<sup>b</sup> Rideal: Disinfection and preservation of food. 1903, p. 153.

<sup>c</sup> Bull. Nat. Board Health U. S. A. 1881, v. 3, p. 21.

<sup>d</sup> Ueber disinfection. Mitt. kais. gesundh., 1881, p. 28.

The following table shows the results of his experiments with anthrax spores exposed in greater percentages of zinc chloride:

Percentage of zinc chloride.	Time of exposure in days.					
	1	3	5	10	20	30
5.....	+	+	+	+	+	+
2.....	+	+	+	+	+	+

The mark + indicates that the spores taken from the zinc chloride solution on the respective days had undiminished power to develop.

Anthrax spores exposed on silk threads in a percentage of 1:200 of zinc chloride dissolved in blood serum retained their power to develop after 48 hours' exposure equally as well as the controls. This he observed under the microscope.

From his experiments he concludes that  $ZnCl_2$  in a percentage of 1:20 has no power to influence anthrax spores, so far as their development is concerned, after an exposure of one week.

He further concludes that it is a fact that zinc chloride has no marked power to prevent micro-organic growth, and that it is, indeed, incomprehensible to him that any considerable disinfecting value could be ascribed to this substance.

F. Bouillat<sup>a</sup> recognized zinc chloride as a good antiseptic, but found that a 5 per cent solution did not kill the spores of anthrax. To blood serum and egg albumen diluted with two to four times their volume of water he added zinc chloride and observed that it coagulated the albumen, forming an insoluble zinc albuminate, and that, provided enough of the salt be added to unite with the whole of the albumen, no growth can take place. In his experiments with this zinc albuminate he also observed that it has some power for inhibiting bacterial growth and the development of foul odors.

Miquel<sup>b</sup> placed chloride of zinc in his class 3 of substances as "strongly antiseptic" and states that 1.9 parts in 1,000 will prevent putrefaction in neutral beef bouillon. He places it in the same class with permanganate of potash, chloroform, cyanide of potash and carbolic acid. He also states that 1.9 parts of zinc chloride is equivalent to 3.2 parts of carbolic acid for preventing putrefactive changes in neutral beef bouillon.

Sternberg<sup>c</sup> says: "In the writer's experiments 1:200 destroyed *Micrococcus Pasteuri* in 2 hours, but a 2 per cent solution was required to kill pus cocci in the same time; spores of *Bacillus anthracis* were not destroyed by 2 hours' exposure in a 10 per cent solution, but a

<sup>a</sup> Beiträge zur lehre von der antiseptis, 1882.

<sup>b</sup> Les organismes vivants de l'atmosphère. 1883.

<sup>c</sup> Text-book of bacteriology, 1891, p. 195.



solution of 5 per cent killed the spores of *Bacillus subtilis* in the same time."

The disinfecting solution devised by Dr. C. B. Dudley<sup>a</sup> consists of a neutral solution of chlorides of copper and zinc and mercuric chloride put up in 8 ounce bottles and securely corked. Each bottle contains 2,400 grains of zinc chloride, 120 grains of cupric chloride, 10.5 grains of mercuric chloride, and 10 drops of an equal mixture of terbene and spirits of turpentine. According to Sedgwick,<sup>b</sup> who examined it for its efficiency, the chloride of copper is added to fix the sulphureted hydrogen and the zinc chloride on account of its deodorizing properties. Sedgwick found the disinfectant an efficient germicide, killing the spores of *B. subtilis* and *B. anthracis* in a few minutes, but did not observe that the zinc chloride materially contributes to its value as a disinfectant.

Sternberg<sup>c</sup> states that solutions of chloride of zinc are largely used in this country and in Europe for disinfecting purposes. It is an excellent antiseptic and deodorant, but its power to destroy disease germs has been very much overestimated. It may, however, be relied upon for the destruction of pathogenic organisms, in the absence of spores, in solutions which contain from 5 to 10 per cent of the salt.

On page 20 of the same essay he further states that "chloride of zinc in 10 per cent solution may be used to disinfect the dejecta of those sick with cholera or typhoid fever, or sulphate of copper in a solution of the same strength (10 per cent), the amount of the solution used being equal to the amount of material to be disinfected."

Under the name of "Burnett's disinfecting fluid"<sup>d</sup> chloride of zinc has had an extensive use in England. This fluid contains from 40 to 50 per cent of zinc chloride.

In Belgium infected clothes are boiled in a solution or a mixture of 240 grams of zinc sulphate and 120 grams of salt dissolved in a pail of water.<sup>e</sup>

The diversity of opinion and results of investigators concerning the value of chloride of zinc as a disinfectant is apparent, and it was for the purpose of determining the real merits of chloride of zinc as a deodorant, antiseptic, and germicide that this work was undertaken.

*Acknowledgment.*—To Dr. M. J. Rosenau, Director of the Hygienic Laboratory, I am gratefully indebted for assistance and suggestions in the performance of this work.

<sup>a</sup> Pa. R. R. specifications for disinfectant No. 27.

<sup>b</sup> Technology quarterly, v. 6 (2), July, 1893.

<sup>c</sup> Sternberg: Lomb Prize Essay—Disinfection and individual prophylaxis against infectious diseases. p. 19. Revised edition, 1899.

<sup>d</sup> Rideal: Disinfection and preservation of foods, 1903.

<sup>e</sup> Rideal: Disinfection and preservation of food, 1903, p. 345.

According to the United States Pharmacopœia, chloride of zinc ( $\text{ZnCl}_2$ ), as found on the market, is a white, granular, friable, translucent powder or porcelain-like masses, irregular, or molded into pencils, odorless, and of such intensely caustic properties as to make tasting dangerous unless the salt be diluted, when it has an astringent, metallic taste.

It is very deliquescent, and owing to its hygroscopic character should be kept in bottles closed with paraffin. It is possessed of dehydrating powers, removing oxygen and hydrogen from organic matter in the form of water, which probably accounts for what influence it exerts as an antiseptic and germicide. It is soluble in about 0.3 part of water at  $15^\circ \text{C}.$ , forming a clear, viscid solution, which on boiling deposits a basic salt.

It is practically impossible to obtain zinc chloride entirely free from basic salt, and the U. S. Pharmacopœia prescribes the limit of this by directing that 1 drop of hydrochloric acid shall clear up opacity caused in 5 c. c. of a 5 per cent aqueous solution of the salt by the addition of an equal volume of alcohol.

In somewhat aqueous solutions zinc chloride undergoes partial hydrolysis, the precipitate consisting of basic or hydroxy-chlorides, e. g.,  $\text{ZnCl}_2 + \text{H}_2\text{O} = \text{HCl} + \text{Zn} \begin{cases} \text{HO} \\ \text{Cl} \end{cases}$ . This flocculent precipitate can be cleared by the careful addition of dilute hydrochloric acid.

The U. S. Pharmacopœia requires that the official salt contain not less than 99.84 per cent of zinc chloride. This can be determined by dissolving 0.3 gram of dry chloride of zinc in 10 c. c. of water and adding 2 drops of chromate of potash, when it should require 44.1 c. c. of a decinormal silver solution to produce a permanent red color.

When heated to  $115^\circ \text{C}.$  zinc chloride fuses to a clear liquid. At a higher temperature it is partly volatilized in dense, white fumes and, in part, decomposed, leaving a residue of zinc oxide.

The aqueous solution turns blue litmus paper red.

A 5 per cent solution produces no corrosive action on iron, brass, wood, or caoutchouc, and, it is said, does not rot ordinary fabrics, but causes a reddening and smarting sensation when applied to the skin.

Linen threads and hair are not apparently affected after thirty days exposure in a 100 per cent solution of zinc chlorid, but the same strength solution gradually destroys cotton and silk threads. This destruction is so complete at the end of ten or eleven days that no evidence of the presence of these materials in the solution is observable.

The Pharmacopœial solution of zinc chloride (liquor zinci chloridi) has a specific gravity of about 1.535 at  $15^\circ \text{C}.$  and contains about 50 per cent by weight of the salt.

It is practically identical with Burnett's disinfecting fluid.

In the preparation of the percentages of zinc chloride used in the following work 100 per cent solution was first prepared by adding enough distilled water to a given number of grams of the dry zinc chloride to make the same number of cubic centimeters of solution, e. g., to 100 grams of dry zinc chloride sufficient water was added to make 100 c. c. of solution. This solution was kept as a stock from which the weaker dilutions were made.

#### PROPERTIES AS A DEODORANT.

Chloride of zinc is capable of combining with hydrogen sulphide, ammonia, and other offensive products of putrefaction, forming compounds that are comparatively odorless; hence, zinc chloride is a deodorant. It is probable that this property is more or less responsible for its historical reputation as a disinfectant.

Zinc chloride unites with the ammonia given off from organic matter undergoing decay to form ammonium chloride, zinc hydroxide, and various other compounds. With hydrogen sulphide it unites to form zinc sulphide, but the union is so feeble that it is rather easily broken up again into hydrogen sulphide, etc. As the sulphide of copper is a more stable compound than the sulphide of zinc, chloride of copper is sometimes used for the purpose of fixing the hydrogen sulphide.

Experiments were performed to ascertain the value of chloride of zinc as a deodorant. Its properties as a deodorant were also observed and noted in the experiments that were conducted to determine its antiseptic powers.

Erlenmeyer flasks were partly filled with definite quantities of sewage (human excreta, stable manure, etc.) and varying definite quantities of zinc chloride added in order to determine its deodorizing powers. As this property is a more or less variable one depending upon time, temperature, and kind and quantity of organic matter present, one series was kept at room temperature and another placed in the incubating room at a temperature of  $37^{\circ}$  C. The zinc chloride was added in strengths varying from 1:10,000 to 1:50. It was observed that when zinc chloride was added to the above solutions in a proportion as little as 1 part in 10,000 a slight diminution of the odor was at once perceptible. This became more marked as the proportion of zinc chloride was increased until in the strength of 1:300 only slight odor could be detected. In a strength of 1:200 the odor was practically destroyed.

In the series allowed to stand at incubator temperature the deodorizing power gradually diminished. At the end of ten days a slight, but not disagreeable, odor was present in dilutions of 1:50, increasing in the higher dilutions until in strengths of 1:300 the odor became

offensive. In the flasks kept at room temperature the changes were similar to but not so marked as in the incubator series.

Zinc chloride is still less efficient as a deodorant in the presence of organic matter of vegetable nature. Some flasks were prepared as above with the addition of particles of vegetable matter, such as cabbage, etc., and kept at room temperature. In the flasks containing dilutions of 1:300 the odor gradually increased as the vegetable matter underwent decay until about the seventh day, when the odor was very offensive. No odor was appreciable in strengths of 1:50.

In dilutions of 1:200 the vegetable matter was preserved at the end of 14 days and the odor was very mild in comparison with the odor from the flasks containing the dilutions of 1:300. In those flasks that contained a less percentage of zinc chloride than 1:200 the degree of odor and the time necessary for decay and disappearance of the vegetable matter varied inversely as the proportion of zinc chloride added.

The deodorizing value of zinc chloride was next determined in the presence of less organic matter than the above experiments. For this purpose ordinary bouillon was inoculated with garden earth containing various organisms and allowed to stand at room temperature, under which conditions chloride of zinc will inhibit the production of foul odors in strengths of about 1:500.

#### ANTISEPTIC PROPERTIES.

For this purpose Erlenmeyer flasks of about 100 c. c. capacity were partly filled with nutrient bouillon and the zinc chloride added in various definite percentages.

When prepared in this way the chloride of zinc produces a white flocculent precipitate, which, on standing, settles to the bottom, leaving the upper portion of the liquid its original straw color and making it possible to observe any bacterial growth that may take place. The quantity of this precipitate varies directly as the quantity of chloride of zinc added.

The flasks having been prepared in this way were abundantly inoculated with different materials rich with organisms such as wisps of hay, fresh stable manure, garden earth, etc., and placed at room temperature. From day to day, up to the end of the fourteenth day, the appearance of molds and bacterial growths was observed. In case of doubt as to bacterial growths, hanging drop preparations were examined under the microscope.



Some of the results may be observed in the following tables:

TABLE A.—*Restraining power of zinc chloride prepared in bouillon and contaminated with wisps of hay—Kept at room temperature.*

[+ means bacterial growth; — means no bacterial growth; s. m. means surface mold; b. m., mold on the bottom; 0 means no growth of any kind.

Percentage used.	Day on which growth appeared.							
	Second.	Third.	Sixth.	Seventh.	Tenth.	Eleventh.	Twelfth.	Fourteenth.
1:1000....	s. m. —	s. m. +	-----	-----	-----	-----	-----	-----
1:500....	s. m. —	s. m. +	-----	-----	-----	-----	-----	-----
1:300....	0	s. m. —	s. m. +	-----	-----	-----	-----	-----
1:200....	0	0	0	s. m. —	-----	s. m. +	-----	-----
1:100....	0	0	0	0	s. m. —	-----	-----	s. m. —
1:75....	0	0	0	0	s. m. —	-----	-----	s. m. —
1:50....	0	0	0	0	0	0	α Mold.	α Mold.
1:45....	0	0	0	0	0	0	0	0
1:40....	0	0	0	0	0	0	0	0
1:35....	0	0	0	0	0	0	0	0

α This was only mold on head of hay and was really not in the solution.

TABLE B.—*Restraining power of zinc chloride prepared in bouillon and inoculated with garden earth—Kept at room temperature.*

Percentage used.	Day on which growth appeared.								
	Second.	Third.	Fourth.	Fifth.	Sixth.	Seventh.	Tenth.	Thirteenth.	Fourteenth.
1:1000....	s. m. +	-----	-----	-----	-----	-----	-----	-----	-----
1:500....	s. m. +	-----	-----	-----	-----	-----	-----	-----	-----
1:300....	0	+	s. m. +	-----	-----	-----	-----	-----	-----
1:200....	0	0	0	s. m. —	s. m. +	-----	-----	-----	-----
1:100....	0	0	0	s. m. —	-----	-----	-----	-----	s. m. —
1:75....	0	0	0	0	0	b. m. —	-----	-----	b. m. —
1:50....	0	0	0	0	0	0	s. m. —	-----	s. m. —
1:45....	0	0	0	0	0	0	s. m. —	-----	s. m. —
1:40....	0	0	0	0	0	0	0	0	b. m. —
1:35....	0	0	0	0	0	0	0	0	0

TABLE C.—*Restraining power of zinc chloride prepared in bouillon and contaminated with stable manure—Kept at room temperature.*

Percentage used.	Day on which growth appeared.								
	Second.	Third.	Fourth.	Fifth.	Eighth.	Tenth.	Eleventh.	Twelfth.	Fourteenth.
1:1000....	s. m. +	-----	-----	-----	-----	-----	-----	-----	-----
1:500....	0	s. m. +	-----	-----	-----	-----	-----	-----	-----
1:300....	0	+	s. m. +	-----	-----	-----	-----	-----	-----
1:200....	0	0	0	s. m. —	s. m. +	-----	-----	-----	-----
1:100....	0	0	0	0	0	b. m. —	-----	-----	b. m. —
1:75....	0	0	0	0	0	0	b. m. —	-----	b. m. —
1:50....	0	0	0	0	0	0	0	b. m. —	b. m. —
1:45....	0	0	0	0	0	0	0	b. m. —	b. m. —
1:40....	0	0	0	0	0	0	0	b. m. —	b. m. —
1:35....	0	0	0	0	0	0	0	0	0

These experiments were repeated and the results verified.

In these experiments it will be observed that the minimum strength of chloride of zinc that inhibited the growth of molds for 14 days was about 1 part in 40, varying slightly with the character of the material used for contamination. The strength that prevented bacterial growth

in the above experiments was between 1:200 and 1:100, while further and similar experiments showed that a percentage of 1:125 inhibits bacterial growth for 21 days, but a growth occurred on the fourteenth day in a percentage of 1:150.

It must be remembered that the antiseptic property of a substance varies more or less with light, character of medium used, and the temperature, the relative importance of these factors increasing in the order named. The influence of diffused light is comparatively feeble. The condition of the medium, independent of the presence of the substance whose antiseptic value is being determined, is an influential factor. A strongly alkaline or acid medium is usually inimical to the growth of bacteria, and the nutrition may not be favorable for the development of the micro-organisms present. A low temperature will inhibit bacterial growth and a high one destroy bacterial life.

Experiments were performed with sewage to determine the quantity of zinc chloride necessary to prevent the development of bacteria. A series of flasks was prepared with an average sample of sewage. Zinc chloride varying in proportion from 1:500 to 1:40 was added to this series of flasks, which were placed at room temperature. A slight cloudiness appeared on the tenth day in the flasks of sewage containing a percentage of 1:500 of zinc chloride.

Another series of flasks was prepared by mixing equal quantities by volume of sewage and tap water. These were also kept at room temperature, and it was found under these conditions that in the percentage of 1:500 of zinc chloride a bacterial growth developed on the fourteenth day.

In a third series of flasks containing sewage and nutrient bouillon in equal volumes and kept at room temperature as above it was found that a bacterial growth developed, indicated by the clouding of the bouillon, on the fifth day in the flask containing zinc chloride in the strength of 1:200, but not in a strength of 1:100 in 14 days.

The organic matter in the flasks referred to above was soon precipitated after adding the zinc chloride, and this was particularly the case when the zinc chloride was in quantity approximately sufficient to inhibit bacterial growth. This precipitate, or residue, was at first brownish in color, but soon became more or less bleached. The bleaching was more apparent in those flasks receiving sufficient zinc chloride to inhibit bacterial development, but was observed to a certain extent in all the flasks, the degree of which varied directly with the quantity of zinc chloride present.

After the precipitate in these flasks settled to the bottom the supernatant liquid was practically clear and transparent, and when the zinc chloride was in quantity sufficient to prevent micro-organic development it gradually assumed a straw color resembling nutrient bouillon.

Further work was done with these same flasks in order to determine

the condition of this supernatant liquid and residue as regards sterility. In order to ascertain this, inoculations were made from the supernatant portion of each flask by transferring with a sterile pipette  $\frac{1}{4}$  or  $\frac{1}{5}$  drops of it to nutrient bouillon and placing it in the incubator at  $37^{\circ}$  C. Considering the absence of growth under these conditions as evidence of sterility, the following tables will show the results obtained with the supernatant portion of the different series of flasks containing various percentages of zinc chloride:

TABLE A.—*Germicidal influence upon the supernatant liquid when zinc chloride is added to ordinary sewage and kept at room temperature.*

[+ means growth; — means no growth.]

Percentage ZnCl <sub>2</sub> .	Time of exposure in days.					
	6.	7.	9.	10.	12.	14.
1:500 .....	+	+	+	+	+	+
1:200 .....	+	+	+	+	+	+
1:100 .....	+	+	+	+	+	—
1:75 .....	+	+	+	+	—	—
1:50 .....	+	+	+	—	—	—
1:45 .....	+	+	—	—	—	—
1:40 .....	+	—	—	—	—	—

TABLE B.—*Germicidal influence upon the supernatant liquid when zinc chloride is added to equal volumes of ordinary sewage and tap water and kept at room temperature.*

Percentage ZnCl <sub>2</sub> .	Time of exposure in days.					
	6.	7.	9.	10.	12.	14.
1:500 .....	+	+	+	+	+	+
1:200 .....	+	+	+	+	+	+
1:100 .....	+	+	+	+	+	—
1:75 .....	+	+	+	+	—	—
1:50 .....	+	+	+	—	—	—
1:45 .....	+	+	—	—	—	—
1:40 .....	+	—	—	—	—	—

TABLE C.—*Germicidal influence upon the supernatant liquid when zinc chloride is added to ordinary sewage and bouillon and kept at room temperature.*

Percentage ZnCl <sub>2</sub> .	Time of exposure in days.			
	6.	7.	10.	14.
1:500 .....	+	+	+	+
1:200 .....	+	+	+	+
1:100 .....	+	+	+	+
1:75 .....	+	+	+	—
1:50 .....	+	+	—	—
1:45 .....	+	+	—	—
1:40 .....	+	—	—	—

From the above results it will be observed, as might be expected, that the microorganisms remained viable longer in the flasks containing the most nutrition, other things being equal. The supernatant portions of the two series of flasks containing no nutrient bouillon were sterile at the end of 14 days in a proportion of zinc chloride of





## BACILLUS TYPHOSUS.

Percentage used.	Time of exposure in minutes.									
	1.	2.	5.	10.	15.	20.	30.	40.	50.	60.
5 .....	+	+	+	+	+	+	+	+	+	+
10 .....	+	+	+	+	+	+	+	+	+	+
15 .....	+	+	-	-	-	-	-	-	-	-
25 .....	+	-	-	-	-	-	-	-	-	-

## VIBRIO CHOLERÆ.

Percentage used.	Time of exposure in minutes.										
	1.	2.	5.	7.	10.	15.	20.	30.	40.	50.	60.
0.5 .....	+	+	+	+	+	+	+	+	-	-	-
1.0 .....	+	+	+	-	+	+	+	-	-	-	-
3.0 .....	+	+	+	+	+	-	-	-	-	-	-
5.0 .....	+	+	+	-	-	-	-	-	-	-	-
10.0 .....	+	-	-	-	-	-	-	-	-	-	-

## BACILLUS DYSENTERIÆ (SHIGA).

Percentage used.	Time of exposure in minutes.							
	1.	4.	5.	10.	20.	30.	50.	60.
5 .....	+	+	+	+	+	+	+	+
10 .....	+	+	+	+	+	+	+	-
15 .....	+	+	+	+	-	-	-	-
25 .....	+	+	-	-	-	-	-	-

## BACILLUS DIPHThERIÆ.

Percentage used.	Time of exposure in minutes.							
	1.	3.	5.	10.	20.	30.	50.	60.
3 .....	-	+	+	+	+	+	+	+
5 .....	+	+	+	+	+	+	+	-
10 .....	+	+	-	-	-	-	-	-
25 .....	+	-	-	-	-	-	-	-

## STAPHYLOCOCCUS PYOGENES AUREUS.

Percentage used.	Time of exposure in minutes.							
	5.	10.	15.	20.	30.	40.	50.	60.
5 .....	-	+	+	+	+	+	+	+
10 .....	-	+	+	+	+	+	+	-
15 .....	+	+	+	+	-	-	-	-
25 .....	+	+	+	+	-	-	-	-

## STAPHYLOCOCCUS EPIDERMIS ALBUS.

Percentage used.	Time of exposure in minutes.								
	1.	3.	5.	10.	20.	30.	40.	50.	60.
3 .....	+	+	+	+	+	+	+	+	+
5 .....	+	+	+	+	+	+	+	-	-
10 .....	+	+	+	+	+	+	-	-	-
15 .....	+	+	+	+	-	-	-	-	-
25 .....	+	+	-	-	-	-	-	-	-

Controls all grew within 24 hours.



TABLE B.—Germicidal results when the *B. pyocyaneus* was exposed in percentages of zinc chloride prepared in distilled water.

Percentage ZnCl <sub>2</sub> .	Time of exposure.							
	10 min-utes.	20 min-utes.	30 min-utes.	2 hours.	3 hours.	5 hours.	7 hours.	18 hours.
5 .....	+	+	+	+	+	+	+	-
10 .....	-	+	+	+	-	-	-	-
25 .....	+	+	-	-	-	-	-	-

TABLE B1.—Same as Table B, when nutrient bouillon was used instead of distilled water.

Percentage ZnCl <sub>2</sub> .	Time of exposure.							
	10 min-utes.	20 min-utes.	30 min-utes.	2 hours.	3 hours.	5 hours.	7 hours.	18 hours.
5 .....	+	+	+	+	+	+	+	+
10 .....	+	-	+	+	+	+	-	-
25 .....	+	+	-	-	-	-	-	-

These results, confirmed by repeating several times, show that when zinc chloride is prepared in nutrient bouillon its germicidal value is not appreciably influenced by the organic matter contained therein as compared with its value when prepared in distilled water.

As has already been stated, zinc chloride produces a heavy white precipitate when added to nutrient bouillon. Consequently experiments were performed to determine the relative germicidal properties of this precipitate as compared with those of the clear transparent portion that remains above. A 10 per cent solution of zinc chloride in nutrient bouillon was prepared and allowed to settle. The clear supernatant portion was then siphoned off and 10 c. c. of it placed in a test tube. Ten cubic centimeters of the precipitate was placed in another test tube. Both tubes were then inoculated with a 24-hours-old agar culture of *Bacillus pyocyaneus*, after which plants at definite intervals were made from each tube into nutrient bouillon in the usual way.

The results of the inoculations made every hour show that the *Bacillus pyocyaneus* was killed within 3 hours in the tube containing the supernatant portion, and within 4 hours in the tube containing the precipitate, indicating that the supernatant portion has slightly greater germicidal powers than the precipitated portion. A similar experiment in which *Bacillus typhosus* was substituted for *Bacillus pyocyaneus* shows that this organism was killed in both tubes within 2 hours.

#### GERMICIDAL INFLUENCE OF ZINC CHLORIDE ON SEWAGE.

For this work an average sample of sewage was selected. Definite quantities were placed in Erlenmeyer flasks and heavily inoculated with a watery suspension of a 24-hours-old agar culture of *Bacillus pyocyaneus*. Various definite percentages of zinc chloride were then

added and the flasks kept at room temperature. At definite intervals inoculations were made into bouillon and Dunham's solution in the usual manner and placed in the incubator at 37° C.

In the following results P means that there was a growth of *pyocyaneus*; + means that there was a bacterial growth, but no evidence of *pyocyaneus*; - means no growth.

Percentage ZnCl <sub>2</sub> .	Time of exposure.										
	1 hour.	2 hours	3 hours	5 hours	1 day.	2 days.	3 days.	4 days.	5 days.	7 days.	14 days.
Control.....	P	P	P	P	P	P	P	P	P	P	+
0.2.....	P	P	P	P	P	P	P	P	P	P	+
1.0.....	P	P	P	P	P	P	P	P	P	P	+
2.0.....	P	P	P	P	-	+	-	-	+	+	+
5.0.....	P	P	-	-	+	-	-	-	+	+	+
10.0.....	+	+	-	-	+	-	-	-	+	+	+

*Bacillus pyocyaneus* was used in these experiments as a control, so to speak, on account of the ease with which its growth can be observed.

As its power of resisting the action of germicides compares very favorably with that of the nonspore-bearing pathogenic organisms it possesses value for control purposes in the disinfection of feces. When exposed to the action of zinc chloride prepared in sewage—with its host of various micro-organisms—the viability of the *B. pyocyaneus* is diminished as compared with its viability when exposed in the same strengths of zinc chloride prepared in distilled water. This difference is rather marked and may be due to a combination of factors.

The sewage was slightly acid and of course contained many other organisms which in time may have overrun the *pyocyaneus*, as it had disappeared from the control flask at the end of 14 days.

By referring to the preceding tables it will be observed that *B. pyocyaneus* was killed within 3 hours in the flask of sewage containing 5 per cent of zinc chloride, while it was not destroyed after 7 hours' exposure in an aqueous solution of the same strength.

The organisms that were still viable after 1 or 2 days' exposure in the flasks of sewage containing the larger percentages of zinc chloride appeared to be principally spore-bearing organisms.

It was next desired to determine the viability of some of the pathogenic organisms, such as cholera, typhoid fever, etc., when exposed to the action of zinc chloride in sewage.

As the overgrowth of ordinary sewage bacteria makes this determination in sewage well-nigh impossible, a sample of sewage similar to that used in the above experiments was sterilized with steam under pressure. After sterilization it was placed in flasks as in the foregoing experiment and heavily inoculated with 24-hours-old agar cultures of different pathogenic organisms and the various percentages of zinc chloride added.



Inoculations into bouillon at definite intervals were made and placed in the incubator at 37° C. Following are the results with the different organisms used:

*Results when B. dysenteriae (Shiga) was exposed in percentages of zinc chloride prepared in sterile sewage.*

[+ means growth; - means no growth.]

Percentage ZnCl <sub>2</sub>	Time of exposure in hours.					
	1.	2.	3.	5.	7.	24.
1.....	+	+	+	+	+	+
2.....	+	+	+	+	+	-
5.....	+	+	+	+	+	-

*Results when B. typhosus was exposed in percentages of zinc chloride prepared in sterile sewage.*

Percentage ZnCl <sub>2</sub> .	Exposure in hours.				
	½.	1.	2.	3.	5.
1.....	+	+	+	+	-
2.....	+	+	-	-	-
5.....	+	+	-	-	-

*Results when Vibrio cholerae was exposed in percentages of zinc chloride prepared in sterile sewage.*

Percentage ZnCl <sub>2</sub> .	Exposure in hours.				
	½.	1.	2.	3.	5.
1.....	+	+	+	+	-
2.....	+	-	-	-	-
5.....	-	-	-	-	-

*Results when B. pyocyaneus was exposed in percentages of zinc chloride prepared in sterile sewage.*

Percentage ZnCl <sub>2</sub> .	Exposure in hours.				
	1.	2.	3.	5.	72.
1.....	+	+	+	+	+
2.....	+	+	+	+	+
5.....	+	+	+	-	-

Controls were all viable at the end of 3 days.

Sterilization of sewage of course alters its natural composition to a certain extent, but it is the only practical way in which the viability of the pathogenic organisms used in these experiments with zinc chloride in sewage can be determined with any degree of accuracy.

A comparison of the results obtained under these conditions show that they do not differ materially from those obtained under similar conditions when distilled water is used instead of sterile sewage.

## EFFECTS OF ZINC CHLORIDE UPON SPORE-BEARING ORGANISMS.

Experiments were performed with 7-days-old agar cultures of *B. subtilis* and *B. anthracis*. A hanging-drop preparation of each culture was examined before it was used to see that it contained many spores.

Preparations of zinc chloride varying from 5 to 100 per cent were prepared in distilled water and 20 c. c. of each strength placed in a large test tube. It may be well to state here that by a 100 per cent solution of zinc chloride is meant a solution made by adding enough distilled water to a given number of grams of dry zinc chloride to make the same number of cubic centimeters of solution. The dilutions were made accordingly. For the purpose of exposing the spores in these solutions of zinc chloride different methods were employed. In some experiments a watery suspension of the organisms to be used was made and added to the different solutions of zinc chloride, after which plants from each tube into nutrient bouillon were made at definite intervals and placed in the incubator at 37° C.

The results show that the spores of *B. subtilis* were still viable after 4 days' exposure in a 100 per cent solution of zinc chloride, but produced no growth when transplanted after 5 days' exposure in the same strength. The spores of *B. anthracis* were capable of multiplying when transplanted into bouillon after an exposure of 7 days in a 25 per cent solution of zinc chloride.

An objection to the above mode of procedure is that when the inoculated solutions of zinc chloride are to be kept for a long period, say a month, some of the organisms that adhere to the sides of the test tube above the liquid, and consequently are not immersed in it, are liable to be carried over in making the plants from time to time and give erroneous results as to the germicidal value of the substance being determined or the viability of the organism under test.

This is more likely to occur if the contents of the tube are shaken up before making the inoculations.

By using a sterile pipette for making the inoculations and carefully carrying it to the bottom of the tube, as was done in the above experiments, this possible source of error is reduced to a minimum. The principal objection to the use of the pipette for this purpose is that too much of the zinc-chloride solution is carried over.

The silk-thread method was also used for exposing the organisms in the zinc-chloride solutions and proved more satisfactory than the preceding method. Sterile silk threads about 1 inch long were soaked in a thick watery suspension of the organism to be used and about 20 threads placed in each strength of zinc chloride. Inoculations were made at definite intervals by carefully transferring a thread to nutrient bouillon and placing in the incubator at 37° C

In the more concentrated solutions so much of the zinc chloride is carried over on the thread that it was found better to use two tubes of bouillon for each thread, one being used to wash out most of the zinc chloride, after which the thread is planted in another tube. Both tubes were then incubated at 37° C. The results obtained with the tubes in which the threads were placed after washing were much more uniform and satisfactory than those in which the threads were washed.

The following are the tabulated results with 7 days old spores of *B. anthracis* on silk threads exposed in various percentages of zinc chloride prepared in distilled water:

[+ means growth; -, no growth.]

Percentage ZnCl <sub>2</sub> .	Time of exposure in days.					
	5.	10.	15.	20.	25.	40.
5 .....	+	+	+	+	+	+
10 .....	+	+	+	+	+	+
25 .....	+	+	+	+	+	+
50 .....	+	+	+	+	+	+

The spores of *B. subtilis* on silk threads exposed in a 100 per cent solution of zinc chloride were viable at the end of the tenth day, after which time the silk threads were so completely destroyed by the action of the zinc chloride that further planting was impossible.

By substituting linen threads, which are not destroyed by a 100 per cent solution of zinc chloride, for silk threads in the above experiment it was found that the spores of *B. subtilis* were still viable after thirty days exposure.

#### SUMMARY AND CONCLUSIONS.

Chloride of zinc has had more or less reputation as a deodorant, antiseptic, and disinfectant for many years, but it has gradually been realized that it was much overrated, particularly as an antiseptic and disinfectant, and its use for these purposes is becoming more and more limited.

It is used as an ingredient of some proprietary preparations found on the market and vaunted for their disinfectant powers, but its rôle is principally that of a deodorant. Even as a deodorant there are certain objections or limitations to its use, but for the sanitarian it is the only property of any practical value that it possesses.

When zinc chloride is added to sewage in dilutions as high as 1:10,000 a diminution of offensive odors is appreciable; but this effect is only transitory. As the percentage of zinc chloride is increased its deodorizing effect becomes more marked and more permanent. It is a fairly reliable deodorant in proportions varying from 1:500 to 1:200, but the exact percentage to be used in each case depends upon the kind and condition of material to be acted upon.

The union of zinc chloride with hydrogen sulphide is not stable enough to recommend it for the neutralization of this offensive compound.

The antiseptic powers of zinc chloride are feeble.

Prepared in nutrient bouillon a percentage of about 1:40 is required to inhibit the growth of molds for 14 days, while under the same conditions a strength of 1:125 is required to inhibit for the same length of time bacterial development.

Added to ordinary sewage, zinc chloride will inhibit bacterial growths in proportions varying from 1:500 to 1:200, depending to a certain extent upon the quantity of nutrition present.

Chloride of zinc can not be relied upon for destroying micro-organic life, as the *B. coli communis* is not killed in a 5 per cent solution in 1 hour's exposure, and it takes 10 minutes for a 25 per cent solution to kill the same organism.

It requires 30 minutes for a 25 per cent solution to kill *Staphylococcus pyogenes aureus*.

Spores of *B. subtilis* are not killed in a 100 per cent solution in 30 days, and the spores of *B. anthracis* are not killed in a 50 per cent solution in 40 days.

Zinc chloride has some properties as a deodorant to recommend it favorably, but its antiseptic and germicidal powers are comparatively feeble, which, with its cost and caustic properties, practically eliminate it from the useful and reliable disinfectants.



Jos. Goldberger

TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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HYGIENIC LABORATORY.—BULLETIN No. 23.

AUGUST 1, 1905.

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CHANGES IN  
THE PHARMACOPŒIA OF THE  
UNITED STATES OF  
AMERICA

*EIGHTH DECENNIAL REVISION.*

(Official from September 1, 1905.)

By

REID HUNT

and

MURRAY GALT MOTTER.



WASHINGTON:  
GOVERNMENT PRINTING OFFICE.

1905.

NOTICE TO LIBRARIANS AND BIBLIOGRAPHERS CONCERNING THE SERIAL  
PUBLICATIONS OF THIS LABORATORY.

The Hygienic Laboratory was established in New York, at the Marine Hospital on Staten Island, August, 1887. It was transferred to Washington, with quarters in the Butler Building, June 11, 1891, and a new laboratory building, located in Washington, was authorized by act of Congress, March 3, 1901.

The following *bulletins* [Bulls. Nos. 1-7, 1900 to 1902, Hyg. Lab., U. S. Mar.-Hosp. Serv., Wash.] have been issued:

- No. 1.—Preliminary note on the viability of the *Bacillus pestis*. By M. J. Rosenau.  
No. 2.—Formalin disinfection of baggage without apparatus. By M. J. Rosenau.  
No. 3.—Sulphur dioxide as a germicidal agent. By H. D. Geddings.  
No. 4.—Viability of the *Bacillus pestis*. By M. J. Rosenau.  
No. 5.—An investigation of a pathogenic microbe (*B. typhi murium* Danyz) applied to the destruction of rats. By M. J. Rosenau.  
No. 6.—Disinfection against mosquitoes with formaldehyd and sulphur dioxid. By M. J. Rosenau.  
No. 7.—Laboratory technique: Ring test for indol, by S. B. Grubbs and Edward Francis; Collodium sacs, by S. B. Grubbs and Edward Francis; Microphotography with simple apparatus, by H. B. Parker.  
By act of Congress, approved July 1, 1902, the name of the "United States Marine-Hospital Service" was changed to the "Public Health and Marine-Hospital Service of the United States," and three new divisions were added to the Hygienic Laboratory.  
Since the change of name of the Service the bulletins of the Hygienic Laboratory have been continued in the same numerical order, as follows:  
No. 8.—Laboratory course in pathology and bacteriology. By M. J. Rosenau. (Revised edition March, 1904.)  
No. 9.—Presence of tetanus in commercial gelatin. By John F. Anderson.  
No. 10.—Report upon the prevalence and geographic distribution of hookworm disease (uncinariasis or anchylostomiasis) in the United States. By Ch. Wardell Stiles.  
No. 11.—An experimental investigation of *Trypanosoma lewisi*. By Edward Francis.  
No. 12.—The bacteriological impurities of vaccine virus; an experimental study. By M. J. Rosenau.  
No. 13.—A statistical study of the intestinal parasites of 500 white male patients at the United States Government Hospital for the Insane; by Philip E. Garrison, Brayton H. Ransom, and Earle C. Stevenson. A parasitic roundworm (*Agamomermis culicis* n. g., n. sp.) in American mosquitoes (*Culex sollicitans*); by Ch. Wardell Stiles. The type species of the cestode genus *Hymenolepis*; by Ch. Wardell Stiles.  
No. 14.—Spotted fever (tick fever) of the Rocky Mountains; a new disease. By John F. Anderson.  
No. 15.—Inefficiency of ferrous sulphate as an antiseptic and germicide. By Allan J. McLaughlin.  
No. 16.—The antiseptic and germicidal properties of glycerin. By M. J. Rosenau.  
No. 17.—Illustrated key to the trematode parasites of man. By Ch. Wardell Stiles.  
No. 18.—An account of the tapeworms of the genus *Hymenolepis* parasitic in man, including reports of several new cases of the dwarf tapeworm (*H. nana*) in the United States. By Brayton H. Ransom.

TREASURY DEPARTMENT.

Public Health and Marine-Hospital Service of the United States.

WALTER WYMAN, Surgeon-General.

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Authority to use for comment the Pharmacopœia of the United States of America, Eighth Decennial Revision, in this volume, has been granted by the Board of Trustees of the United States Pharmacopœial Convention, which Board of Trustees is in no way responsible for the accuracy of any translation of the official weights and measures, or for any statements as to strength of official preparations.



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## ABBREVIATIONS.

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Br. P. ....	British Pharmacopœia, 1898.
P. G. ....	Pharmacopœia Germanica IV.
T. S. ....	U. S. P. Test Solution.
N. F. ....	National Formulary (1896).



# CHANGES

IN THE

## PHARMACOPŒIA OF THE UNITED STATES OF AMERICA, EIGHTH DECENNIAL REVISION.

(Official from September 1, 1905.)

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By REID HUNT, M. D.,

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### INTRODUCTION.<sup>a</sup>

#### ORIGIN AND SCOPE OF BULLETIN.

The United States Pharmacopœia is the official standard for the U. S. Public Health and Marine-Hospital Service. Drugs purchased for its hospitals and relief stations must conform to the Pharmacopœial requirements. A circular letter, calling the attention of the medical officers and pharmacists of the Service to the many and important changes in the revised edition, was at first contemplated. It was believed that such a letter would aid these officials in their study of the revised Pharmacopœia and facilitate the early adoption of the new names and new preparations. Later, with the approval of the Board of Trustees of the Pharmacopœial Convention, it was decided to publish this information in the form of a bulletin. It is believed that such a bulletin will help the practitioner to a better understanding of the significance of some of the innovations. Being written for physicians, only such changes are discussed in this bulletin as are of interest and use to them, such, for example, as changes in the strength of preparations, changes in name, the additions, etc. For changes relating to methods of preparation, of tests for identity, purity, etc., the reader is referred to the Pharmacopœia itself.

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<sup>a</sup> The authors are greatly indebted to Dr. Daniel Base, of the Division of Pharmacology, for valuable assistance rendered in the preparation of this bulletin.

Special attention is directed to the following points:

1. *Terminology.*—The general plan regarding terminology is expressed in the following extract from the General Principles to be Followed in Revising the Pharmacopœia, adopted by the Pharmacopœial Convention of 1900:

“\* \* \* \* In the case of newly admitted articles it is recommended that such titles be chosen as are in harmony with general usage and convenient for prescribing; but in the case of chemicals of a definite composition a scientific name should be given, at least as a synonym.”

In accordance with this general principle a large number of synthetic remedies have been admitted into the Pharmacopœia, not under their trade or commercial names by which many are well known to the profession, but, in most cases, under names approximating, as closely as practicable, their true chemical names. Thus “Phenacetin” is admitted as *Acetphenetidinum*, a name which shows at once that this substance belongs to the great group of phenetidin compounds. “Aristol” is admitted as *Thymolis Iodidum*, a name showing that this substance is an iodine compound of thymol. While a few of these new names may at first lead to some confusion, it is certain that they will ultimately greatly simplify not only the terminology, but also our understanding of the nature and use of such substances. For example, at present the same chemical compound is sometimes put on the market under a variety of commercial names. Thus, hexamethylene tetramine is sold under at least seven different names, most of which refer in a vague way to some supposed therapeutic value of the drug, and not to its chemical nature. The Pharmacopœia admits this substance under the name *Hexamethylenamina* and fixes a standard of purity. By demanding the U. S. Pharmacopœia article the physician is not only assured a product of uniform high quality, but he aids in reducing the multiplicity of names which is so often a source of confusion. Because of the different names under which a given drug is sold, it is no wonder that physicians who have failed to secure the results expected from a certain drug have prescribed it again under a different name, but with the impression that they were trying something new.

The use of the chemical names, as far as practicable, is also a great aid in classifying the compounds which are being put upon the market in such ever increasing numbers. If the physician understands the chemical nature of a comparatively few well-known substances he will more readily see the relations of the new ones to these, and will appreciate how slight many of the modifications are. In fact, notwithstanding the number of the latter, drugs of distinctly new therapeutic properties are rare.

Aside from the evident desirability of having names at least suggesting the chemical nature of the drug, there is another reason for giving preference to the Pharmacopœial names. A substance is often

sold under a fanciful, registered name at a much higher price than under the chemical name. Thus a hardship is worked on pharmacist and patient alike.<sup>a</sup>

The general principle of using, whenever practicable, the true chemical name of a substance has been extended to a number of drugs which were already official in the U. S. Pharmacopœia. Thus, Acidum Carbolicum (U. S. P., 1890) (a name no longer approved in chemical terminology), becomes *Phenol*; the composition of Salol (U. S. P., 1890) is shown by its new official name, *Phenylis Salicylas*, etc.

The "Extracta Fluida" becomes *Fluidextracta*; thus these preparations are separated alphabetically from the other extracts, and much confusion is thereby obviated.

2. *Changes in strength.*—A number of very important changes have been made in the strength of certain preparations. "The International Conference for the Unification of the Formulas of Heroic Medicines," held at Brussels in 1902, recommended that certain preparations of the heroic remedies be made of uniform strength in the pharmacopœias of the different countries. The present revision of the U. S. Pharmacopœia has accepted nearly all of the recommendations adopted by this conference. The tincture of aconite, for example, is reduced from 35 per cent to 10 per cent, the tincture of cantharides is increased from 5 per cent to 10 per cent, etc. The great majority of tinctures are now of either 10 or 20 per cent strength; the most noteworthy of those of the 10 per cent class, besides aconite and cantharides, just mentioned, are those of digitalis, squill, and strophanthus. These changes have been classified and tabulated for this bulletin.

The increase in the scope of pharmacopœias is an interesting chapter in the history of medicine. Before the publication of the first U. S. Pharmacopœia (in 1820) various European pharmacopœias were the chief standards for this country, although the United States Army, the Massachusetts Medical Society, and the New York Hospital had previously issued pharmacopœias of more than local importance. It was not until 1864 that there was a national British Pharmacopœia; prior to that year three pharmacopœias were in use in Great Britain—the London, the Edinburgh, and the Dublin. The U. S. Pharmacopœia, in adopting the suggestions of the Brussels Conference, is the first pharmacopœia to acquire an international scope.<sup>b</sup>

<sup>a</sup>To obviate this unnecessary increase of expense to the patient a Government order was recently issued in Germany directing the official physicians to the poor to prescribe drugs under their Pharmacopœial instead of under their registered names.

<sup>b</sup>The growing tendency to give wider recognition to official standards is well shown by the fact that, in several States, drugs not in the U. S. Pharmacopœia are deemed adulterated if they do not conform to the standards of purity of foreign pharmacopœias.



3. *Additions.*—There are 117 additions in the Eighth Decennial Revision of the U. S. Pharmacopœia; among these are representatives of all classes of drugs. There is, for instance, a larger number of synthetic remedies than ever before. The principles involved in the pharmacopœial terminology of these have already been discussed. The active principles of a number of drugs have been admitted; this permits of more accurate dosage and their use obviates the necessity of administering inert and often undesirable constituents of the crude drug. New salts of well-known drugs have been admitted on account of their greater stability or solubility. Inasmuch as the discovery of diphtheria antitoxin is perhaps the greatest achievement in therapeutics in the last quarter of a century, the *Serum Antidiphthericum* is a very notable addition to the Pharmacopœia; not only is this substance made official but a definite American standard for it has been fixed.

A class of additions deserving careful consideration by the medical profession is represented by certain of those combinations of well-known drugs which in recent years have become popular with physicians and also with the laity. Some of these preparations are extensively sold under various trade names, and the manufacturers have not always made public their constituents: the same name is sometimes applied by different manufacturers to different combinations. Recognizing the demand for such preparations a number of them have been admitted into the Pharmacopœia, and the proportions of the ingredients fixed, thereby giving physicians the opportunity of securing uniform preparations, the constituents of which are of known strength and purity.

The introduction of these various preparations reduces to a very small number those extra-pharmacopœial drugs which the conservative, well-informed physician will desire to prescribe. There are undoubtedly a few drugs not in the Pharmacopœia which many physicians have found to be of distinct value; most of these are protected by patents and could not be admitted under the rules formulated by the Pharmacopœial Convention. The pharmacopœial preparations, however, will in most cases meet the needs of physicians who are accustomed to consider carefully the chemical nature and the physiological action of a drug before they venture to use it, and who know how rarely a distinctly new drug with real advantages over those already in use is discovered.

4. *Assay processes.*—A noteworthy feature of the revised Pharmacopœia, and one which places it at the head of the pharmacopœias of the world in this respect, is the introduction of a large number of assay processes for important drugs of vegetable origin. An examination of the tables given in this bulletin (pp. 65-66) will show that standards of strength and methods for confirming them have been



introduced for over fifty important official preparations for which no such requirements were made in the 1890 Pharmacopœia.

Before the introduction of assay methods the pharmacist and physician were compelled to judge the quality of drugs largely by their appearance; from this it was possible to determine in many cases whether medicinal plants, for example, had been collected and cared for in a way which would *probably* preserve their therapeutic virtues. In many cases, however, the physician was compelled to rely solely upon the therapeutic test. Great credit is due those manufacturers who for years have been perfecting processes of assay and placing upon the market preparations of definite strength of many of the most important drugs.

The introduction into the Pharmacopœia of such a large number of these assay processes will now insure a more general uniformity in the purity, strength, and therapeutic action of pharmacopœial preparations than ever before, and the entire medical profession is under lasting obligations to the Committee of Revision who have labored so long to perfect as nearly as possible these assay methods. Unfortunately there still remain a number of pharmacopœial preparations for which no definite method of chemical analysis or assay has been devised. Among these may be mentioned the *Serum Antidiphthericum*, already referred to. Another group embraces certain galenicals, the active principles of which are as yet either not sufficiently known or are incapable of isolation and assay by present methods. Although care in the selection and in the manufacture of the materials will in many cases insure preparations of therapeutic value, yet, for the careful standardization of such, recourse is had to physiological methods; but physiological methods of standardization were specifically barred from the Pharmacopœia by the Pharmacopœial Convention of 1900. The reasons for this are obvious; assay processes introduced into the Pharmacopœia are such as every well-equipped pharmacist is able to apply. It is not to be expected, however, that even the best-equipped pharmacist should have the theoretical knowledge, the technical training, and the material facilities for biological and physiological investigations. Recognizing the increasing demand for standardized preparations, certain manufacturing establishments have been equipped not only with pharmaceutical and chemical laboratories of the most approved type, but with biological laboratories as well, the work and products of which are a credit alike to commercial enterprise and to genuine scientific progress.

5. *Purity rubric.*—Whenever practicable a minimum degree of purity has been fixed and requirements established which exclude objectionable impurities.

6. *Doses.*—The Pharmacopœial Convention instructed the Committee of Revision “to state the average approximate (but neither a

minimum nor a maximum) dose for adults," and further directed it to declare "that neither this Convention, nor the Committee of Revision created by it, intends to have these doses regarded as obligatory on the physician or as forbidding him to exceed them whenever in his judgment this seems advisable." A table of these doses has been compiled and inserted in this bulletin.

#### RELATION OF PHYSICIANS TO THE PHARMACOPŒIA.

A few words may be added regarding the relation of the physician to the Pharmacopœia. The U. S. Pharmacopœia had its origin in the medical profession, and the early editions were entirely the work of physicians. Although so vitally interested in the Pharmacopœia—for in many cases it is the physician's sole legal guarantee of the quality of the drugs he uses—and although medical men are always represented on the Committee of Revision, the medical profession as a whole can scarcely be said to give the publication the support it deserves; physicians often prescribe proprietary drugs or articles under commercial names when a greater familiarity with the Pharmacopœia would show that there are official preparations of similar character but of more uniform composition. The authority of the Pharmacopœia, however, is steadily increasing; nearly half the States have made it the legal standard for drugs, and whenever a "pure drug bill" is proposed it is assumed, almost as a matter of course, that the U. S. Pharmacopœia is to be the standard by which the quality of drugs is to be judged. Despite the fact that there may, and of necessity always will, be certain minor imperfections in the Pharmacopœia, it is and will remain the leading standard; and no one questions the imperative need of such a standard.

The need of such a standard for drugs intended for the use of physicians is all the more evident when it is remembered that some manufacturers who do make standard pharmacopœial preparations nevertheless frankly admit that they put upon the market other preparations of the same substance by no means of pharmacopœial standard but under names almost identical with the pharmacopœial names. These manufacturers claim that, when the official article is not specifically designated, popular demand and commercial competition justify this procedure. The possible dangers in such a course must at once be apparent, and this practice is one of the reasons for the legal requirement in many States that any article sold under a pharmacopœial name must conform to pharmacopœial standards.

The Pharmacopœia is moreover the chief bulwark of one of the most time-honored principles of the medical profession, namely, that there must be no secrets about the drugs used in the treatment of disease. Upon this question, that physicians must have full knowledge of all the constituents and of all the properties of the drugs they prescribe,

there can be no compromise. The physician should never forget that he is the sole judge of what is suitable for his patient.<sup>a</sup>

Not only does the individual patient often suffer, but real progress in therapeutics is delayed by the use of remedies as to the composition of which the physician has but imperfectly informed himself; in many cases were the real nature of the drug made known the physician would see the folly of using it. The mythical character of the virtues claimed for some "special combinations" has been repeatedly shown by chemical analysis.<sup>b</sup> Thus some of the remedies advertised to physicians under fanciful names, with very vague descriptions of their composition but with full directions for use, have been shown to be nothing but mixtures of some of the best-known U. S. Pharmacopœia drugs.

The Pharmacopœia is often criticised for retaining and admitting drugs which many physicians regard as useless. It should be remembered, however, that the Pharmacopœia is (and under our form of government must be) representative, as well as conservative; the framers endeavor to make it reflect the actual demands of the medical profession.<sup>c</sup>

<sup>a</sup>That the assurances as to the virtues of secret or semi-secret preparations, although made in good faith and supported by high authority, are not a sufficient safeguard against dangerous accidents, is illustrated by the following case: Some manufacturers who prepared certain tinctures with methyl alcohol attempted to justify their departure from recognized pharmaceutical methods by claiming that methyl alcohol is a better solvent of some of the constituents of ginger than is ethyl alcohol, and this claim, as well as the contention that methyl alcohol is not more toxic than ethyl alcohol, was supported in court by the testimony of high official chemists; the plaintiff in the case in question (a physician whose sight was destroyed by the methyl alcohol) thought when he bought this preparation that he was buying an article made according to the Pharmacopœia.

<sup>b</sup>See, for example, the reports of the Council on Pharmacy and Chemistry of the American Medical Association.

<sup>c</sup>The scope of the Pharmacopœia is well described in the following words of H. C. Wood, President of the U. S. Pharmacopœial Convention (Pop. Sci. Monthly, Jan., 1905, p. 279):

"A common, fallacious belief is that Pharmacopœial recognition means that the drug recognized is of value; the fact is that the United States and other Pharmacopœias have in them numerous drugs of very little use. The nature or *motif*, so to speak, of a Pharmacopœia is not to distinguish between worthy and worthless drugs, but to see that a drug which is asked for is, as sold by the apothecary, pure, and that proper preparations of uniform strength are made by the apothecary.

"The question which the framers of a Pharmacopœia ask themselves is not, Is this drug of value, but Is there a demand for it by the profession of medicine? If five thousand doctors in the United States believed brick dust to be a valuable remedy and habitually used it, brick dust would have to go into the Pharmacopœia. Witch-hazel is probably as active and as useful as is brick dust, but witch-hazel is a fad and is enormously called for, and so witch-hazel must go into the Pharmacopœia. The Pharmacopœia exists for the purpose of requiring the apothecary to give, in the first place, pure brick dust or pure witch-hazel when asked for; and, in the second place, uniform preparations of these remedies."

If obsolete drugs are retained or new ones of proved value fail to gain admission to the Pharmacopœia it is because the medical profession of the country fails, through lack of concerted action (as by means of the national or local medical societies) to make their wishes sufficiently clear.<sup>a</sup>

No account of the Eighth Decennial Revision of the Pharmacopœia would be complete without an expression of the gratitude which all physicians must feel to the Committee of Revision who, with no motives other than their interest in higher standards, have labored so long and well to perfect as nearly as may be the U. S. Pharmacopœia.

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<sup>a</sup> When the Pharmacopœial Convention of 1900 met, only five medical organizations presented recommendations and suggestions for the revision of the Pharmacopœia.



## ADDITIONS TO THE PHARMACOPŒIA.

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### ACETONUM.

#### Acetone.



“A liquid containing not less than 99 per cent by weight of absolute acetone.” (U. S. P.)

Chemically, acetone is dimethyl-ketone ( $\text{CH}_3\text{COCH}_3$ ). It is present to a considerable extent in crude wood alcohol.

**Properties.**—Clear, colorless, mobile, neutral liquid, inflammable, and having an ethereal odor and taste. Specific gravity, 0.790 ( $25^\circ\text{C}$ .); boiling point,  $56.5^\circ\text{C}$ . Miscible with water and alcohol in all proportions. An excellent solvent for fats, resins, rubber, etc. Iodoform is formed when acetone is slightly warmed with an alkali and iodine (basis of method for determining acetone in diabetic urine, etc.); it also yields iodoform with an alcoholic solution of iodine and ammonia (Gunning’s test; difference from alcohol). Acetone forms with nitroprussiate of soda and sodium hydroxide a reddish-brown color, which passes into purple or violet on acidifying with acetic acid (Legal’s test).

**Use.**—Acetone is used extensively in the manufacture of chloroform, iodoform, and sulphonmethane (q. v.). A number of oleoresins (aspidium, capsicum, ginger, lupulin, and pepper) formerly prepared (U. S. P., 1890) with ether are now prepared with acetone, as the latter is neither so inflammable nor so expensive as the former.

Acetone seems to be slightly more poisonous than ethyl alcohol; the symptoms caused by the two are, generally speaking, similar.

**Caution.**—It should be kept in well-stoppered bottles remote from lights or fire.

**Related Compounds.**—When a phenyl radical ( $\text{C}_6\text{H}_5$ ) takes the place of one of the methyl groups in acetone, the resulting compound is phenyl-methyl-ketone ( $\text{C}_6\text{H}_5\text{COCH}_3$ ), also known as acetophenone. This has been used as a hypnotic under the name of *Hypnone*. It is a liquid above  $20.5^\circ\text{C}$ . *Malarine* is a condensation product of acetophenone and paraphenetidin (see Acetphenetidin). It is usually employed in the form of the citrate.

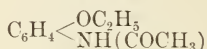
*Salacetolum* is a salicylic acid ester of acetol which is an alcohol ( $\text{CH}_3\text{COCH}_2\text{OH}$ ) derived from acetone; proposed as an antirheumatic.

Acetoacetic acid, also called diacetic acid ( $\text{CH}_3\text{COCH}_2\text{COOH}$ ), which may be looked upon as acetone in which a hydrogen atom has been replaced by the acid group ( $\text{COOH}$ ), is found in the urine in many cases of diabetes mellitus. It is thought that one source of acetone found in diabetic urine is the decomposition of diacetic acid.

### ACETPHENETIDINUM.

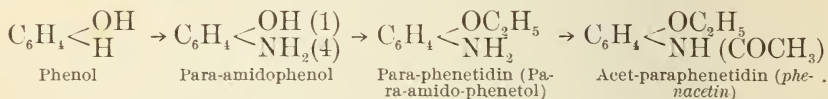
#### Acetphenetidin.

(*Phenacetin.*)



This substance is generally known by the trade name *phenacetin*; official in the British, German, and Swiss Pharmacopœias as Phenacetinum; also called para-acetphenetidin.

**Chemistry.**—The derivation of acetphenetidin is shown by the following formulas:



It may be regarded as acetanilide ( $\text{C}_6\text{H}_4 \left\langle \begin{array}{l} \text{H} \\ \text{NH}(\text{COCH}_3) \end{array} \right.$ ) in which one hydrogen atom is replaced by the ethoxy group ( $\text{OC}_2\text{H}_5$ ).

**Character.**—“White, glistening, crystalline scales, or fine crystalline powder, odorless, and tasteless.”

**Solubility.**—Slightly soluble in water (1:925), much more so in boiling water (1:70), and still more in alcohol (1:12).

**Purity.**—Occasionally adulterated with acetanilide, which may be recognized by the following Pharmacopœial test:

“If 0.1 Gm. of Acetphenetidin be boiled with 10 Cc. of water it should yield a solution which, when cooled and filtered, should not become turbid upon the addition of bromine T. S. [1 per cent solution] in slight excess (absence of acetanilide).”

For other tests, see the Pharmacopœia and Kebler, Lyman F.: *Adulterated drugs and chemicals*, U. S. Dept. Agric., Bur. Chemistry, Bull. No. 80, 1904.

**Incompatibility.**—Incompatible with phenol, chloral hydrate, iodine, salicylic acid, and oxidizing agents.

**Dose.**—“Average dose: 0.500 Gm. = 500 milligrammes ( $7\frac{1}{2}$  grains).” (U. S. P.)

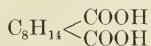
**Caution.**—The German Pharmacopœia states that not more than 3 Gm. (45 grains) should be given in the course of a day. Special caution should be observed when acetphenetidin is prescribed in combination with other drugs of similar physiological action; thus, acetanilide and acetphenetidin should not be combined in full dose of each.

Excreted in the urine as amidophenol or amidophenetol, which gives a red color with ferric chloride; also causes appearance of a reducing substance.

**Similar Compounds.**—This is the representative of a very large number of similar compounds known as the phenetidid series. These are derived from para-amidophenol  $\left( C_6H_4 \left\langle \begin{array}{l} OH \text{ (1)} \\ NH_2 \text{ (4)} \end{array} \right. \right)$  by replacing the hydrogen atom of the hydroxyl group and one or both of the hydrogen atoms of the amido ( $NH_2$ ) group by alkyl or acid radicals. Thus, *lactophenin* is formed when the lactyl group ( $COCH(OH)CH_3$ ) is introduced into para-phenetidid instead of the acetyl ( $CH_3CO$ ) group:  $C_6H_4 \left\langle \begin{array}{l} OC_2H_5 \\ NHCOCH(OH)CH_3 \end{array} \right.$ . *Sedatin*,<sup>a</sup> *apolyisin*, *citrophen*, *kryofin*, *malakin*, *salophen*, *saliphen*, *phenocoll*, *salocoll*, etc., are similar compounds. The physiological action of all these substances is fundamentally the same. These compounds, as well as acetphenetidid itself, are contained in many migraine and headache powders. *Chinophenin* and *eupyrine* are also phenetidid compounds.

### ACIDUM CAMPHORICUM.

#### Camphoric Acid.



“A dibasic organic acid obtained by the oxidation of camphor.” Official under same name in the German Pharmacopœia.

Of the various camphoric acids known, only the dextro-rotatory is official. It is prepared by oxidizing camphor with nitric acid.

**Character.**—Colorless, odorless crystalline plates, or a crystalline powder having an acid, bitter taste. Melting point,  $187^\circ C$ . It forms easily soluble salts with the alkalies.

**Solubility.**—Difficultly soluble in cold water (1:125), more readily in boiling water (1:10); readily soluble in alcohol; soluble in fatty oils (1:50).

**Purity.**—Should not have the odor of camphor; tested by the U. S. Pharmacopœia method should be free from nitric acid.

**Action.**—The general symptoms produced by camphoric acid are similar to those caused by camphor, but the latter is much more powerful. Used as an antihydrotic in doses of 1 to 2 Gm. and (in solution) as a local astringent in the nose, throat, and bladder. As it is but slightly soluble in water, it has been recommended in making solutions to add 11 per cent of alcohol for each per cent of camphoric acid.

**Dose.**—“Average dose: 1 Gm. (15 grains).” (U. S. P.)

*Guakamphol* is a combination of Guaiacol and Camphoric Acid.

<sup>a</sup>The name *sedatin* has also been used as a synonym for antipyrine.

**ACIDUM HYDRIODICUM DILUTUM.****Diluted Hydriodic Acid.**

HI

“A solution of hydriodic acid containing not less than 10 per cent by weight of the absolute acid, and about 90 per cent of water.”

This is a reintroduction, the preparation having been admitted to the U. S. Pharmacopœia of 1860, but dismissed on account of the difficulty of preserving it.

In the present preparation there is a small quantity of hypophosphorous acid. This acts as a preservative by reducing any iodine set free to hydriodic acid. The method of preparing it (for which see the Pharmacopœia) is that recommended in the 1890 U. S. Pharmacopœia in connection with the preparation of Syrupus Acidi Hydriodici; the latter is now prepared from the Acidum Hydriodicum Dilutum. The method is simple and requires no special apparatus or chemicals.

**Character.**—A clear, colorless liquid, odorless and having an acid taste. It should not become colored on keeping. Miscible in all proportions with water or alcohol.

**Dose.**—“Average dose: 0.5 Cc. (8 minims).” (U. S. P.)

**Caution.**—“Should be kept in small, amber-colored, glass-stoppered bottles, protected from the light.”

**ACIDUM HYPOPHOSPHOROSUM.****Hypophosphorous Acid.**HPH<sub>2</sub>O<sub>2</sub>

“A liquid composed of 30 per cent by weight of absolute hypophosphorous acid and 70 per cent of water.”

**Properties.**—A colorless, odorless liquid having an acid taste. Miscible in all proportions with water. It is a powerful reducing agent, precipitating metallic silver from solutions of silver nitrate, calomel from corrosive sublimate, etc.; when heated with copper sulphate a yellow precipitate of copper hydride is formed (difference from phosphorous acid).

It is used in the preparation of Acidum Hypophosphorosum Dilutum.

**Incompatibilities.**—Incompatible with arsenical salts, and in general with substances that are more or less easily reduced.

**ACIDUM TRICHLORACETICUM.****Trichloroacetic Acid.**CCl<sub>3</sub>.COOH

“A monobasic organic acid usually obtained by the oxidation of hydrated chloral with nitric acid.”

**Properties.**—White, deliquescent, rhombohedral crystals, having a slight, characteristic, mild pungent odor.



Very soluble in water and alcohol; in the latter, part of the acid is changed into the ester.

The aqueous solution on boiling is decomposed with the formation of chloroform and carbon dioxide:  $\text{CCl}_3\text{COOH} = \text{CHCl}_3 + \text{CO}_2$ .

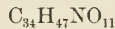
Ten parts of trichloroacetic acid and 1 part of water form a liquid known as acidum trichloroaceticum liquefactum; it is often dispensed in this form (cf. Phenol Liquefactum).

It precipitates proteids and is used as a reagent for the detection of albumin in urine and milk.

**Caution.**—"Should be kept in dark, amber-colored, well-stoppered bottles in a cool place." It is far stronger than acetic acid and should be used with great caution.

### ACONITINA.

#### Aconitine.



An alkaloid obtained from Aconite. Official in the Br. P.

The chemical structure of aconitine is analogous to that of atropine and cocaine; like the latter it undergoes partial decomposition when boiled for some time with water.

**Properties.**—Colorless or white rhombic tables or prisms, odorless, permanent in the air, and producing in extremely diluted solutions a characteristic tingling sensation when brought in contact with the mucous membrane of the tongue or lips. The alkaloid itself should never be tasted, and its solution only when largely diluted, and then with the utmost caution.

Very slightly soluble in water (1:3200), much more so in alcohol (1:22).

Aconitine was formerly in the U. S. Pharmacopœia, but was dropped in 1880 owing to the variable composition of the article then on the market. At present there are on the market, in addition to the crystalline aconitine, an amorphous aconitine and an eclectic "aconitin." The greatest caution should be observed not to confuse these preparations, as they differ considerably in composition.

Aconitine is the most powerful drug in the Pharmacopœia; death is reported to have resulted from 0.5 milligramme ( $\frac{1}{16}$  grain).

**Dose.**—"Average dose: 0.00015 Gm. = 0.15 milligramme ( $\frac{1}{400}$  grain)." (U. S. P.)

Aconitine is contained in the Oleatum Aconitinæ of the National Formulary.

### ADEPS LANE.

#### Wool-Fat.

Adeps Lanæ, Br. P.; Adeps Lanæ anhydricus, P. G. "The purified fat of the wool of sheep, freed from water." The Hydrous Wool-Fat, which contains "not more than 30 per cent of water," is still

retained in the Pharmacopœia; if this be heated on the water bath, with stirring, until it ceases to lose weight, it is converted into Adeps Lanæ.

In making certain ointments, the water contained in hydrous wool-fat is objectionable; for such preparations Adeps Lanæ is preferable.

### ETHYLIS CARBAMAS.

#### Ethyl Carbamate.

(*Urethane.*)



Ethyl Carbamate is defined as: "An ester of carbamic acid obtained by the reaction of ethyl alcohol upon urea (carbamide) or one of its salts." Reaction:  $\text{CO} < \begin{array}{l} \text{NH}_2 \\ \text{NH}_2 \end{array} + \text{HOC}_2\text{H}_5 = \text{CO} < \begin{array}{l} \text{NH}_2 \\ \text{OC}_2\text{H}_5 \end{array} + \text{NH}_3$

**Character.**—"Colorless, columnar crystals or scales, odorless, and having a cooling saline taste."

**Solubility.**—Soluble in less than one part of water, and in 0.6 part of alcohol.

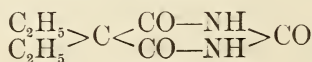
**Dose.**—"Average dose: 1 Gm. (15 grains)." (U. S. P.)

Larger doses do not as a rule increase the hypnotic effect, as the (NH<sub>2</sub>) group stimulates the central nervous system in somewhat the way that ammonia (NH<sub>3</sub>) does. Both Ethyl Carbamate (*urethane*) and *hedonal* (see below) frequently fail to produce sleep, probably owing to the stimulating action of the (NH<sub>2</sub>) group.

**Caution.**—Should be kept in well-stoppered bottles.

This substance, generally known simply as *urethane*, is a member of a series of compounds called urethanes. They are esters of carbamic acid  $\text{CO} < \begin{array}{l} \text{NH}_2 \\ \text{OH} \end{array}$  which in turn is derived from carbonic acid  $\text{CO} < \begin{array}{l} \text{OH} \\ \text{OH} \end{array}$  by the substitution of the amido group (NH<sub>2</sub>) for one hydroxyl group (OH). Carbamic acid is not known in the free state, but only in the form of its salts. The ammonium salt is a constituent of the Pharmacopœial Ammonium Carbonate.

**Related Products.**—Closely allied to ethyl carbamate are: *hedonal* (methylpropylcarbinolurethane =  $\text{CO} < \begin{array}{l} \text{NH}_2 \\ \text{O}-\text{CH} < \begin{array}{l} \text{CH}_3 \\ \text{C}_3\text{H}_7 \end{array} \end{array}$ ), *euphorine* or *phenylurethane* ( $\text{CO}(\text{NHC}_6\text{H}_5)\text{OC}_2\text{H}_5$ ), *neurodin*, *thermodin* (*phenacetin-urethane*), etc. One of the latest additions to this group is the *veronal* of Emil Fischer and von Mering; this is diethylmalonylurea:



## ÆTHYLIS CHLORIDUM.

## Ethyl Chloride.



Ethyl Chloride is "a haloid derivative, prepared by the action of hydrochloric acid gas upon absolute ethyl alcohol." Also known as *chelene* or *kelene*.

**Character.**—"Colorless, mobile, very volatile liquid, having a characteristic, rather agreeable odor and a burning taste." It boils at a temperature of  $12.5^\circ$  to  $13^\circ$  C.

**Solubility.**—Slightly soluble in water, readily in alcohol.

**Purity.**—"If 10 Cc. of ethyl chloride, while cold, be dissolved in alcohol, and a few drops of silver nitrate T. S.  $\left[ \frac{\text{N}}{10} \text{AgNO}_3 \right]$  be added, no turbidity should be produced (absence of hydrochloric acid)."

Although ethyl chloride is usually used as a local anæsthetic, it is contained in the following mixtures intended for general anæsthesia:

<i>Anæsthol</i>	<table style="border: none; border-collapse: collapse;"> <tr> <td style="padding-right: 10px;">Ethyl chloride . . . . .</td> <td style="padding-right: 10px;">17 parts</td> <td rowspan="3" style="border-left: 1px solid black; padding-left: 10px; vertical-align: middle;">} by weight.</td> </tr> <tr> <td style="padding-right: 10px;">Chloroform . . . . .</td> <td style="padding-right: 10px;">36 parts</td> </tr> <tr> <td style="padding-right: 10px;">Ether . . . . .</td> <td style="padding-right: 10px;">48 parts</td> </tr> </table>	Ethyl chloride . . . . .	17 parts	} by weight.	Chloroform . . . . .	36 parts	Ether . . . . .	48 parts
Ethyl chloride . . . . .	17 parts	} by weight.						
Chloroform . . . . .	36 parts							
Ether . . . . .	48 parts							
<i>Somnoform</i>	<table style="border: none; border-collapse: collapse;"> <tr> <td style="padding-right: 10px;">Ethyl chloride . . . . .</td> <td style="padding-right: 10px;">60 parts</td> <td rowspan="3" style="border-left: 1px solid black; padding-left: 10px; vertical-align: middle;">} by weight.</td> </tr> <tr> <td style="padding-right: 10px;">Methyl chloride . . . . .</td> <td style="padding-right: 10px;">35 parts</td> </tr> <tr> <td style="padding-right: 10px;">Ethyl bromide . . . . .</td> <td style="padding-right: 10px;">5 parts</td> </tr> </table>	Ethyl chloride . . . . .	60 parts	} by weight.	Methyl chloride . . . . .	35 parts	Ethyl bromide . . . . .	5 parts
Ethyl chloride . . . . .	60 parts	} by weight.						
Methyl chloride . . . . .	35 parts							
Ethyl bromide . . . . .	5 parts							

(Jour. Amer. Med. Assoc., April 22, 1905, p. 1303.)

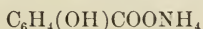
"*Anæsthol* (Speier)" is a mixture of ethyl chloride and methyl chloride for local anæsthesia. *Anestyl* and *coryl* are also mixtures of ethyl chloride and methyl chloride.

**Caution.**—Very inflammable; should not be used in proximity to a gas flame or fire. It should be preserved in hermetically sealed glass tubes in a cool place.

As a permanent opacity may result when freezing mixtures come in contact with the cornea, Merz-Weigandt (Hirschberg's Festschrift, 1905, p. 187) emphasizes the necessity of caution when using ethyl chloride about the head.

## AMMONII SALICYLAS.

## Ammonium Salicylate.



**Character.**—"Colorless, lustrous, monoclinic prisms or plates, or a white crystalline powder, odorless, and having at first a slightly saline, bitter taste, with a sweetish aftertaste. Permanent in dry air." The concentrated aqueous solution reddens blue litmus.

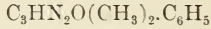
**Solubility.**—Very soluble in water (0.9 part), slightly less so in alcohol (2.3 parts).

Dose.—“Average dose: 0.250 Gm. = 250 milligrammes (4 grains).”  
(U. S. P.)

“Should be kept in well stoppered bottles, protected from heat and light.”

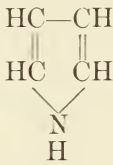
### ANTIPIRYRINA.

#### Antipyrine.

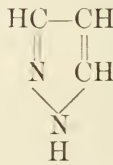


Official in the Austrian and Swiss Pharmacopœias as Antipyrinum; now official in the German Pharmacopœia as Pyrazolonum phenyldimethylicum (formerly as Antipyrinum); in the British as Phenazonum, and in the French as Analgésine. Other names that have been applied to it are *anodynin*, *metozin*, *oxydimethylchinizin*, *parodyn*, *phenazon*, *phenylon*, *pyrazolin*, *sedatin*.

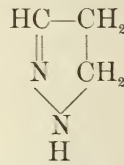
**Chemistry.**—Chemically it is phenyldimethylisopyrazolon; its derivation may be seen from the following formulas:



Pyrrrol



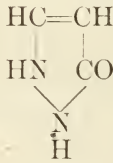
Pyrazol



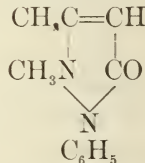
Pyrazolin



Pyrazolon



Iso-pyrazolon



Dimethyl-phenyl-  
iso-pyrazolon

It is not obtained directly from the mother substance isopyrazolon, but is built up synthetically by condensation of phenylhydrazine with acetoacetic ether, and methylation of the product.

**Character.**—“A colorless, almost odorless, crystalline powder, or tabular crystals, with a slightly bitter taste.”

**Solubility.**—Soluble in less than 1 part of water, and in 1 part of alcohol.

**Purity.**—“Two Cc. of an aqueous solution of Antipyrine (1 in 100) mixed with an equal volume of nitric acid assumes a yellowish color, passing to crimson on warming (distinction from acetanilide and acetphenetidin).”

“On warming 0.1 Gm. of Antipyrine with sodium hydroxide T. S. [Liq. Sodii Hydroxidi] and again warming after the addition of chloroform, the disagreeable odor of phenyl-isocyanide should not be developed (absence of acetanilide).”



**Incompatibilities.**—Hager's Handbuch der pharmaceutischen Praxis calls attention to the incompatibility of Antipyrine with a large number of substances and the production therewith of unexpected changes; among these may be mentioned:

(1) Antipyrine and nitrous acid, or substances which can evolve nitrous acid, as, for instance, Amylis Nitris and Spiritus Ætheris Nitrosi; a green color results from the formation iso-nitroso-antipyrine.

(2) Antipyrine and Mercurous Chloride (calomel); a very poisonous organic mercury compound is formed in a mixture of these substances.

(3) Antipyrine and Phenol, even in dilute aqueous solution, form an oily mass.

(4) Antipyrine and Sodii Salicylas, when rubbed together in powder, form a pasty mass; in solution they do not seem to affect each other.

(5) Antipyrine and Betanaphthol give a moist mixture.

(6) Antipyrine and Hydrated Chloral, rubbed together, form an oil which no longer gives the reactions of the components.

(7) Tannic acid precipitates Antipyrine as a tannate.

On the other hand, Antipyrine increases the solubility in water of caffeine and the quinine salts.

**Allied Compounds.**—Antipyrine unites with resorcin to form *resopyrin*, with salicylic acid to form *salipyryn*, with chloral hydrate to form *hypnal* and other compounds. *Pyramidon* is a dimethylamido substitution product of antipyrine. *Ferripyryn* is a combination of ferric chloride and antipyrine. Many other compounds are known. Antipyrine is a constituent of many "migraine powders."

**Dose.**—"Average dose: 0.250 Gm. = 250 milligrammes (4 grains)." (U. S. P.)

**Caution.**—On account of the wide range of incompatibilities already indicated, the greatest caution should be observed in combining antipyrine with other substances.

#### AQUE.

#### Waters.

#### Medicated Waters.

"The Medicated Waters, when prepared from volatile oils, are intended to be, as nearly as practicable, saturated solutions, which must be clear, and free from solid impurities."

This is a new title under which various methods of preparing official waters of volatile oils are briefly outlined. In the method especially recommended by the Pharmacopœia, in a number of cases, the solution of the volatile oils is facilitated by the use of purified talc, instead of by precipitated calcium phosphate, as in U. S. Pharmacopœia, 1890.

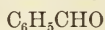
**AQUA HAMAMELIDIS.****Hamamelis Water.**

The final product here is a distillate, while the old *Extractum Hamamelidis Fluidum* is a percolate now designated *Fluidextractum Hamamelidis Foliorum*.

The aqua contains about 15 per cent of alcohol.

**Dose.**—“Average dose: 8 Cc. (2 fluidrachms).” (U. S. P.)

This preparation is almost identical with *Aqua Hamamelidis Spirituosa*, N. F.

**BENZALDEHYDUM.****Benzaldehyde.**

“Produced artificially or obtained from natural oil of bitter almond or other oils, and containing not less than 85 per cent of pure benzaldehyde.”

**Properties.**—“Colorless, strongly refractive liquid, having a bitter-almond-like odor and a burning, aromatic taste.” “Sparingly soluble in water (1:300); soluble in all proportions, in alcohol, ether, and fixed and volatile oils.”

Synthetic benzaldehyde is usually prepared from benzylchloride or benzylidenechloride; unless carefully purified, such benzaldehyde will contain chlorinated products (hence the U. S. P. test for these; cf. also *Oleum Amygdalæ Amaræ*).

Unless properly prepared the benzaldehyde obtained from the natural oil of bitter almond may contain prussic acid (hence the U. S. P. test for this substance).

Benzaldehyde is the principal constituent of natural oil of bitter almond. The U. S. Pharmacopœia, Eighth Decennial Revision, demands that the official oil of bitter almond contain not less than 85 per cent of benzaldehyde. The natural oil of bitter almond also contains hydrocyanic acid; the Eighth Decennial Revision demands that the official oil contain not less than 2 per cent nor more than 4 per cent of hydrocyanic acid. The commercial natural oils of bitter almond contain from 1.5 to 11 per cent, or more, of hydrocyanic acid; hence (unless the hydrocyanic acid has been removed) they should be used with great caution as flavoring agents.

**Dose.**—“Average dose: 0.03 Cc. ( $\frac{1}{2}$  minim).” (U. S. P.)

**Caution.**—It should be kept in small, amber-colored, well-stoppered bottles, as it is readily oxidized to benzoic acid; the latter change occurs more rapidly with the pure benzaldehyde than with the natural oil of bitter almond.

Nitrobenzene is an oil having an odor very much like that of oil of bitter almond; it is known as “artificial oil of bitter almond,” or “essence of mirbane.” It is sometimes used as a substitute for the oil of bitter almond in the manufacture of soap, cheap confectionery, etc. It is very poisonous.

## BENZINUM PURIFICATUM.

### Purified Petroleum Benzin.

For certain purposes—as, for instance, the preparation of deodorized tincture of opium—the ordinary U. S. P. Benzinum (Petroleum Benzin or “petroleum ether”) is not sufficiently pure, hence the introduction of the purified product. The process of purification provided by the Pharmacopœia is designed to remove some of the heavier hydrocarbons and foreign, malodorous substances.

Petroleum ether is occasionally used in the preparation of mixtures for the production of general anæsthesia. Schleich has recommended three different mixtures for use in operations of short, moderate, and considerable duration, respectively:

	I.	II.	III.
Chloroform .....	45.0	45.0	30.0
Ether .....	180.0	150.0	80.0
Petroleum ether (boiling point 60–65° C.) .....	15.0	15.0	15.0
	⏟	⏟	⏟
Boiling point of the mixture.....	38° C.	40° C.	42° C.

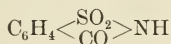
As Schleich's theory turns entirely on the boiling point of the resulting mixture, it may be well to remember that the boiling point of Benzinum (U. S. P.) is given at 45°–60° C. Schleich's mixtures are said, however, to have no constant boiling point.

(For other general anæsthetic mixtures, based upon Schleich's researches, see under *Æthylis Chloridum*.)

## BENZOSULPHINIDUM.

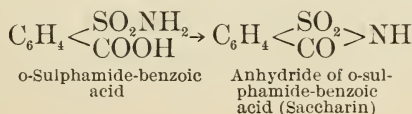
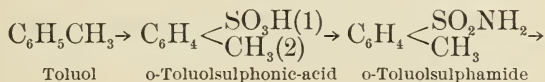
### Benzosulphinide.

#### Saccharin.



Official as *Saccharinum* in the Austrian and Swiss Pharmacopœias, as *Glusidum* (Gluside) in the British Pharmacopœia, and as *Acide anhydroorthosulfamide-benzoïque* in the French. It is variously known as *glucosimide*, *saccharol*, *saccharinol*, *saccharinose*, *agucarine*, etc.

**Chemistry.**—Chemically it is the anhydride of ortho-sulphamide-benzoic acid (benzoyl sulphonic-imide). Its derivation from toluol (from which it is usually made) is shown by the following formulas:



Saccharin was discovered in 1879 by Ira Remsen and C. Fahlberg.

**Character.**—A white, crystalline powder, nearly odorless, having an intensely sweet taste even in dilute solutions. The sweet taste may be recognized in a dilution of 1:100,000, as compared with cane sugar 1:200.

**Solubility.**—Soluble in 250 parts of water and in 25 parts of alcohol; more so in boiling water (1:24). It behaves like a strong acid and dissolves readily in alkalies; the sodium salt ( $C_6H_4 \left\langle \begin{smallmatrix} CO \\ SO_2 \end{smallmatrix} \right\rangle NNa$ ) is known as *soluble saccharin* or *krystallose*.

The Liquor Saccharini of the National Formulary is a solution of saccharin in sodium bicarbonate and alcohol.

There are a number of preparations on the market, such as *antidiabeticin*, which contain saccharin.

**Dose.**—“Average dose: 0.200 Gm. = 200 milligrammes (3 grains).” (U. S. P.)

*Dulcin* or *sucrol*, another very sweet substance, is para-phenetolcarbamid; *Savin* is a similar product.

## BERBERIS.

### Berberis.

The rhizome and roots of *Berberis aquifolium* and other species of Berberis. *Berberis aquifolium* is known as Oregon Grape Root. It contains an alkaloid, berberine, which is also found in Menispermum (a drug dropped from the present Revision), Calumba, Hydrastis, and other drugs.

A Fluidextract of Berberis has also been admitted into the U. S. Pharmacopœia.

**Dose.**—“Average dose: 2 Gm. (30 grains).” (U. S. P.)

## BISMUTHI SUBGALLAS.

### Bismuth Subgallate.

Official in the German Pharmacopœia as Bismutum subgallicum; also known as *dermatol*.

**Composition.**—Although somewhat variable in chemical composition, Bismuth Subgallate approximates the following formula:  $C_6H_2(OH)_3CO_2Bi(OH)_2$ , which contains 56.49 per cent of bismuth oxide ( $Bi_2O_3$ ). The U. S. Pharmacopœia demands that it contain not less than 52 per cent, nor more than 57 per cent, of pure bismuth oxide.

**Character.**—An amorphous, bright yellow powder, odorless, tasteless, and permanent in the air.

**Solubility.**—Insoluble in water and alcohol, and in very dilute mineral acids. Readily soluble with decomposition in hydrochloric, nitric, and sulphuric acids, if these be heated. Alkalies dissolve it readily,



forming clear, yellow-colored solutions, which rapidly change to deep red.

**Dose.**—"Average dose: 0.250 Gm. = 250 milligrammes (4 grains)." (U. S. P.)

It is used in general for the same purposes as the subnitrate.

### BISMUTHI SUBSALICYLAS.

#### Bismuth Subsaliicylate.

Official under the names of Bismutum subsaliicylicum (P. G.), Bismutum salicylicum (Swiss), Bismuthi Salicylas (Br. P.). The composition varies somewhat, but is approximately  $C_6H_4(OH)CO_2BiO$ . The U. S. Pharmacopœia requires that it yield not less than 62 per cent, nor more than 64 per cent, of pure bismuth oxide.

**Character.**—"A white, or nearly white, amorphous or crystalline powder, odorless, tasteless, and permanent in the air."

**Solubility.**—Almost insoluble in water; on prolonged boiling with water, a more basic salt is formed through the splitting off of free salicylic acid. Alcohol or ether extracts salicylic acid, with decomposition of the salt. Acids decompose it, with separation of a white, flocculent precipitate of salicylic acid.

**Dose.**—"Average dose: 0.250 Gm. = 250 milligrammes (4 grains)." (U. S. P.)

**Other Unofficial Bismuth Compounds.**—A large number of bismuth compounds have been proposed for medicinal use in the last few years. The following may be mentioned as examples: *Airol* (bismuth oxyiodo-subgallate), *bismal* (bismuth methylene digallate), *bismutol* ("bismuth sodium phosphate salicylate"), *crurin* (quinolin bismuth sulphocyanate), *eudoxin* (bismuth tetraiodo-phenolphthalein), *iodogallicin* (bismuth oxyiodide methyl-gallol), *orphol* (bismuth betanaphthol), other phenolates, the benzoate, the chrysophanate (*dermol*), the cinnamylate (*heteroform*), the cresolate, the lactate, the bilactomonotannate (*lactanine*), the phenolsulphonate, the tannate, and similar salts; also proteid compounds, as the peptonate; compounds with resorcin, pyrogallol (*helcosol*), etc.

### BROMOFORMUM.

#### Bromoform.



Official in the German Pharmacopœia as Bromoformium. This is tribrommethane, being entirely analogous in composition to chloroform and iodoform.

**Character.**—A heavy, transparent, colorless, mobile liquid having an ethereal odor and a penetrating, sweetish taste resembling chloroform.

**Solubility.**—Only slightly soluble in water, but readily in alcohol and ether. Specific gravity at 25° C., 2.808. It is only slightly volatile at ordinary temperature, boils at 148° C., and solidifies at 6° C.

Absolute bromoform is decomposed in presence of light and air more rapidly than chloroform. The addition of 4 per cent of alcohol, as in the case of chloroform, will preserve bromoform for months. When decomposed, bromine is set free, which colors the liquid yellowish red.

**Dose.**—“Average dose: 0.2 Cc. (3 minims).” (U. S. P.)

**Caution.**—Keep in dark amber-colored, glass-stoppered bottles in a cool place, protected from light.

### CATAPLASMA KAOLINI.

#### Cataplasm of Kaolin.

Introduced in response to a request for an external clay preparation; similar to a number of commercial articles. The constituents are kaolin (57.7 per cent), boric acid, methyl salicylate, glycerin, and small quantities of thymol and oil of peppermint.

### CERATUM RESINE COMPOSITUM.

#### Compound Rosin Cerate.

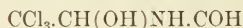
Composed of rosin, yellow wax, suet, turpentine, and linseed oil. For formula and method of preparation see U. S. Pharmacopœia.

Minor changes in the constituents, not however affecting the strength of the active ingredients, have been made in all the cerates with the exception of Ceratum Resinæ.

Ceratum Cantharidis, for instance, should no longer have the odor of oil of turpentine.

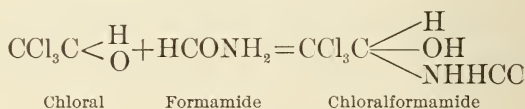
### CHLORALFORMAMIDUM.

#### Chloralformamide.



Chloralum formamidatum (P. G.). Also known as *Chloralamide*, a name which, because it is both inaccurate and misleading (being properly applied to another substance), should not be used.

**Chemistry.**—It is formed by the direct union of anhydrous chloral and formamide, as shown by the following reaction:



Chloral

Formamide

Chloralformamide

**Properties.**—Colorless, lustrous crystals, odorless, and having a somewhat bitter taste.

Soluble in water (1:18.7) and alcohol (1:1.3), readily in glycerin and acetone. It is not affected by dilute acids, but is decomposed, on warming with alkali hydroxides, yielding chloroform; it behaves in this respect like chloral hydrate, and is, hence, incompatible with alkalies. Chloral is formed by its decomposition in the body; the formamide which is formed at the same time is supposed to stimulate the circulation and thus counteract the depression caused by the chloral.

**Dose.**—“Average dose: 1 Gm. (15 grains).” (U. S. P.)

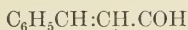
**Caution.**—Keep in amber-colored, well-stoppered bottles. It is easily decomposed in solution by heat; hence heat should not be used in preparing aqueous solutions. Avoid combination in full dose with other drugs of a similar physiologic action, for example, Sulphonethylmethane (*trional*), Sulphonmethane (*sulphonal*), Hydrated Chloral, etc.

**Allied Compounds.**—Chloral, like other aldehydes, forms many addition products more or less comparable with chloralformamide. Thus, with ethyl carbamate, chloral unites to form *uralium*; with dextrose it forms *chloralose*; with antipyrine, *hypnal*; with amylen hydrate, *dormiol*, etc.

*Croton chloral* (Butyl-chloral Hydras, Br. P.) is trichlorobutylaldehyde hydrate ( $\text{CH}_3\text{CHClCCl}_2\text{CH}(\text{OH})_2$ ). Other tri-chlor substitution products recently proposed as hypnotics are *chloretone* or *aneson* (trichloropseudobutylalcohol or *acetone-chloroform*) and *isopral* (trichlorisopropyl alcohol).

## CINNALDEHYDUM.

### Cinnamic Aldehyde.



Obtained from oil of cinnamon or prepared synthetically. It is the chief and essential constituent of oil of cinnamon, and should be present to the extent of about 75 per cent by volume in a good oil.

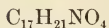
**Character.**—A colorless liquid, having a cinnamon-like odor and a burning, aromatic taste. It may be used for nearly all purposes in place of the official oil of cinnamon. Pure synthetic Cinnamic Aldehyde occurs in the market, and has, to a great extent, displaced the natural oil of cinnamon.

**Solubility.**—Sparingly soluble in water, readily in alcohol, fixed and volatile oils.

**Dose.**—“Average dose: 0.05 Cc. (1 minim).” (U. S. P.)

## COCAINA.

## Cocaine.



Official under same name in the British Pharmacopœia. An alkaloid obtained from several varieties of Coca. Hitherto only the most frequently used salt of Cocaine—the hydrochloride—was official in the U. S. Pharmacopœia.

**Properties.**—Slightly soluble in water (1:600), much more so in alcohol (1:5), more readily in both when warm; insoluble in glycerin.

Cocaine is a methyl compound of benzoylecgonine. When it is boiled with water methyl alcohol is first split off, then benzoic acid; these changes occur more rapidly with dilute acids or barium hydroxide. Conversely cocaine may be built up by introducing the methyl and benzoyl groups into ecgonine (a compound having the empirical formula  $C_9H_{15}NO_3$ ).

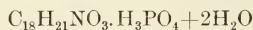
Cocaine is contained in the newly introduced Oleatum Cocainæ.

**Dose.**—“Average dose: 0.030 Gm. = 30 milligrammes ( $\frac{1}{2}$  grain).” (U. S. P.)

**Substitutes for Cocaine.**—A number of synthetic compounds with names suggestive of that of cocaine have recently been introduced as local anæsthetics. Among the best known of these are *beta-eucaine* (the hydrochloride of benzoyl-vinyl-diacetonealkamin); *holocaine*, which may be regarded as a derivative of acetphenetidín (*phenacetin*); *tropacocaine* (benzoylpseudotropein); *nirvanin*, *anæsthin* (para-amido-benzoic acid ester) and *orthoform*, complex derivatives of benzoic acid. *Stovain* is a recent addition to this group.

## CODEINE PHOSPHAS.

## Codeine Phosphate.



Official under same name in the British Pharmacopœia and as Codeinum phosphoricum in the German. Hitherto the free alkaloid alone was official in the U. S. Pharmacopœia.

**Character.**—“Fine, white, needle-shaped crystals or crystalline powder, without odor, and having a bitter taste.”

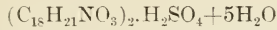
**Solubility.**—Soluble in 2.25 parts of water, 261 parts of alcohol, more so when either is warmed. The aqueous solution has a slightly acid reaction to litmus.

**Dose.**—“Average dose: 0.03 Gm. = 30 milligrammes ( $\frac{1}{2}$  grain).” (U. S. P.)



## CODEINE SULPHAS.

## Codeine Sulphate.



**Character.**—Long, glistening, white needles, prisms or crystalline powder, efflorescent in the air, odorless and having a bitter taste.

**Solubility.**—Soluble in about 30 parts of water and 1,035 parts of alcohol—much more so when either is warmed.

The aqueous solution is neutral to litmus paper.

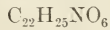
**Dose.**—“Average dose: 0.030 Gm. = 30 milligrammes ( $\frac{1}{2}$  grain).” (U. S. P.)

**Similar Morphine Derivatives.**—Codeine is methylmorphine ( $C_{17}H_{18}(CH_3)NO_3$ ). *Dionine* is ethylmorphine hydrochloride ( $C_{17}H_{17}NO(OH)OC_2H_5HCl + H_2O$ ). *Peronine* is benzylmorphine hydrochloride ( $C_{17}H_{18}NO_3(C_6H_5CH_2)HCl$ ). *Heroine* is diacetylmorphine ( $C_{17}H_{17}NO(C_2H_3O)_2$ ).

Syrupus Codeinæ, N. F. is a 1 per cent solution of Codeine Sulphate in Syrup.

## COLCHICINA.

## Colchicine.



An alkaloid obtained from *Colchicum*. The U. S. Pharmacopœia demands that the official *Colchici Cormus* contain not less than 0.35 per cent and the *Colchici Semen* not less than 0.55 per cent of colchicine. Although classed with the alkaloids, colchicine has an acid reaction.

**Character.**—Pale yellow leaflets or a pale yellow, amorphous powder, turning darker on exposure to light, having an odor suggesting damp hay and a very bitter taste.

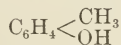
**Solubility.**—Soluble in water (1:22) and readily so in alcohol.

**Incompatibility.**—Colchicine is precipitated from solution by tannic acid.

**Dose.**—“Average dose: 0.0005 Gm. = 0.5 milligramme ( $\frac{1}{200}$  grain).” (U. S. P.)

## CRESOL.

## Cresol.



A mixture of three isomeric cresols obtained from coal tar, freed from phenol, hydrocarbons, and water. Sometimes erroneously called cresylic acid. Cresol is methyl phenol, the three isomeric forms being known chemically as ortho-, meta-, and para-cresol.

**Character.**—A colorless or straw-colored refractive liquid having a phenol-like odor and turning yellowish-brown on prolonged exposure to light.

**Solubility.**—Soluble in water (1:60) and miscible in all proportions with alcohol and glycerin.

Miscible with alkali hydroxide solutions, forming alkali cresolates, homologous with alkali phenolates.

**Purity.**—“If 1 Cc. of cresol be mixed with 1 Cc. of glycerin, a clear solution should be produced, from which, on the addition of 1 Cc. of water, the cresol should completely separate (absence of, and distinction from, phenol).”

**Dose.**—“Average dose: 0.05 Cc. (1 minim).” (U. S. P.)

Much has been written concerning the germicidal and toxic properties of cresol. It is generally held that cresol is more toxic to bacteria than is phenol, but that it is less toxic to higher animals than is the latter. Tollens (Arch. f. exper. Path. u. Pharm., 52, p. 220; 1905) finds that para-cresol is more than twice as toxic for mice as is phenol, ortho-cresol has the same toxicity, while meta-cresol is less toxic. Thus the toxicity of a cresol will depend upon the relative proportion of the three constituents and these seem to vary in different preparations; Tollens finds some specimens to be more toxic than phenol. The U. S. Pharmacopœia does not specifically state the proportions in which the three cresols are present, although it fixes limits for the boiling point, specific gravity, and solubility. A preparation on the market under the name of *tricrosol* (*enterol*) is said to contain 35 per cent of ortho-cresol, 40 per cent of meta-cresol, and 25 per cent of para-cresol; it is soluble to the extent of 2.2 to 2.55 per cent in water. The physiological action of the cresols is almost identical with that of phenol.

The cresols are constituents of coal tar and other crude antiseptic substances. Being but slightly soluble in water, they are often used in the form of emulsions or are dissolved with the aid of salts or of soap. The official Liquor Cresolis Compositus (q. v.) belongs to the latter class; it is practically identical with the Liquor Cresoli saponatus of the German Pharmacopœia and the preparation on the market known as *lysol*. The mixtures known as *creolins* usually contain impure cresol dissolved with the aid of rosin soap; they usually form emulsions when diluted with water. In *solveol* and *solutol* the cresols are held in solution by means of salts. A vast number of similar compounds are upon the market, usually under fanciful names.

*Losophan* and *europfen* are iodine compounds of cresol. *Kresamine* is an aqueous solution of tricresol and ethylenediamine.

#### ELIXIR ADJUVANS.

##### Adjuvant Elixir.

This is made by the addition of Fluidextract of Glycyrrhiza to Aromatic Elixir. An excellent vehicle for bitter or nauseous remedies.

A somewhat similar elixir is to be found in the National Formulary under the same name.

**ELIXIR FERRI, QUININÆ ET STRYCHNINÆ PHOSPHATUM.**

Elixir of Iron, Quinine and Strychnine Phosphates.

This is the official representative of a large class of popular preparations on the market; the formula is an improvement on a similar one in the National Formulary. (See also Glyceritum Ferri, Quininæ et Strychninæ Phosphatum). Some of the commercial elixirs bearing this name are said to contain no phosphoric acid.

**Dose.**—"Average dose: 4 Cc. (1 fluidrachm.)." (U. S. P.) Each fluidrachm contains 0.0647 Gm. (1 grain) of ferric phosphate, 0.0324 Gm. ( $\frac{1}{2}$  grain) of quinine, and 0.001 Gm. ( $\frac{1}{64}$  grain) of strychnine.

**EMPLASTRUM ADHÆSIVUM.**

Adhesive Plaster.

This is to take the place of Emplastrum Resinæ (U. S. P. 1890), from which it differs chiefly in the substitution of rubber for rosin. For formula and method of preparation see the Pharmacopœia.

**EMULSUM OLEI MORRHUÆ.**

Emulsion of Cod Liver Oil.

A standard official preparation, containing 50 per cent of cod liver oil, which might well replace many of the proprietary articles.<sup>a</sup> It may be flavored, to suit the taste, with Oil of Gaultheria, Oil of Bitter Almond, etc.

**Dose.**—"Average dose: 8 Cc. (2 fluidrachms)." (U. S. P.)

**EMULSUM OLEI MORRHUÆ CUM HYPOPHOSPHITIBUS.**

Emulsion of Cod Liver Oil with Hypophosphites.

Similar to the above, but containing the hypophosphites of calcium, potassium, and sodium.

**Dose.**—"Average dose: 8 Cc. (2 fluidrachms)." (U. S. P.)

**EMULSUM OLEI TEREBINTHINÆ.**

Emulsion of Oil of Turpentine.

A 15 per cent (by volume) emulsion of rectified oil of turpentine, containing 5 per cent (by volume) of expressed oil of almond.

**Dose.**—"Average dose: 4 Cc. (1 fluidrachm)." (U. S. P.) One fluidrachm contains about 9 minims of oil of turpentine.

The National Formulary gives a somewhat similar preparation under the name of Emulsio Olei Terebinthinæ.

<sup>a</sup>The character of some of these preparations is shown by the statement (Jour. Amer. Med. Assoc., 44, p. 1943; 1905) that a specimen of a "Tasteless Cod Liver Oil" contained no oil whatever.

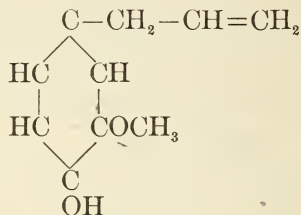
## EUGENOL.

## Eugenol.



An unsaturated, aromatic phenol obtained from Oil of Cloves and other sources.

**Chemistry.**—Chemically it is para-oxy-meta-methoxy-allyl-benzol having the formula:



**Character.**—A colorless, or pale yellow, thin liquid, highly refractive, and having a strongly aromatic odor of cloves and a pungent, spicy taste.

**Solubility.**—Almost insoluble in water, easily soluble in alcohol; should be soluble in 2 parts of 70 per cent alcohol.

This is the chief constituent of Oil of Cloves and may be used instead of the latter; it is also the chief constituent of Oil of Pimenta.

**Dose.**—“Average dose: 0.2 Cc. (3 minims).” (U. S. P.)

**Caution.**—It should be kept in well-stoppered amber-colored bottles, in a cool place, protected from light. Exposure to air causes the oil to become darker and thicker.

**Derivatives.**—Eugenol acetamide and eugenolcarbinol have been recommended as local anæsthetics and antiseptics; eugenol iodide is said to resemble aristol. *Benzeugenol* is the benzoic ether of eugenol.

## EXTRACTUM MALTI.

## Extract of Malt.

This and Maltum (q. v.) are reintroductions into the Pharmacopœia of articles admitted to the 1880 revision but dismissed in 1890; it is contained in the National Formulary. Extractum Malti Fluidum, N. F., is a hydro-alcoholic extract.

**Properties.**—Malt extract consists of easily assimilable carbohydrates—maltose and dextrin—and small quantities of proteids; the ash contains the phosphates of calcium and magnesium. If the malt has not been overheated (by which the diastase would be destroyed), and if the extract is prepared according to the U. S. Pharmacopœia process, the preparation, when fresh, will contain diastase which is an efficient ferment for the conversion of starch into dextrose; the diastatic power, however, rapidly deteriorates on keeping.



Malt extract is contained in numerous infant foods and in malted milks. It is said that much glucose is frequently added to the malt extracts on the market. Many liquid "malt extracts" contain considerable quantities of alcohol, and are very similar to beer.

**Dose.**—"Average dose: 16 Cc. (4 fluidrachms)." (U. S. P.)

It should be kept in well-closed vessels in a cool place.

### EXTRACTUM RHAMNI PURSHIANÆ.

#### Extract of Cascara Sagrada.

Also official in British Pharmacopœia. This solid extract and the Aromatic Fluidextract of Cascara Sagrada are two new preparations of the bark introduced into the Pharmacopœia. Formerly, only the fluid extract was official. One part of the solid extract represents the activity of four parts by weight of the bark.

**Dose.**—"Average dose: 0.250 Gm. = 250 milligrammes (4 grains)." (U. S. P.) This represents 1 Gm. (15 grains) of the bark and is equal to the Pharmacopœial dose of the fluidextract, namely, 1 Cc. (15 minims).

For a recent discussion of the chemistry of Cascara Bark see Jowett, Proc. Amer. Pharm. Assoc., 1904, p. 288.

### EXTRACTUM SCOPOLE.

#### Extract of Scopola.

This is prepared by evaporating, to a pilular consistence, the Fluidextract of Scopola (q. v.). The latter is prepared from the rhizome of *Scopola carniolica*, a plant closely related, in its characters and properties, to belladonna and hyoscyamus.

The U. S. Pharmacopœia demands that the extract of scopola contain 2 per cent of mydriatic alkaloids; for method of assay see Pharmacopœia.

**Dose.**—"Average dose: 0.010 Gm. = 10 milligrammes ( $\frac{1}{8}$  grain)." (U. S. P.)

### EXTRACTUM SUMBUL.

#### Extract of Sumbul.

Prepared from the Fluidextract of Sumbul (q. v.).

In the U. S. Pharmacopœia 1890 the only preparation of Sumbul was the tincture; this is now dropped and the extract and fluidextract admitted.

**Dose.**—"Average dose: 0.250 Gm. = 250 milligrammes (4 grains)." (U. S. P.)

### FLUIDEXTRACTA.

#### Fluidextracts.

In the 1890 Pharmacopœia the solid and the fluid extracts were grouped together; this resulted, at times, in confusion both as to

identity and strength of the several preparations. To avoid this, the new Pharmacopœia gives to the fluidextracts a new alphabetic position, grouping them by themselves; thus *Extractum Aconiti Fluidum* (U. S. P., 1890) becomes *Fluidextractum Aconiti* in the Eighth Decennial Revision. Wherever practicable, assay processes have been introduced, thus ensuring preparations of definite and uniform strength. Many of the solid extracts are directed by the Eighth Revision to be made from the fluidextracts.

Three fluidextracts, those of *Lobelia*, *Sanguinaria* and *Squill*, formerly made with alcohol or (*Sanguinaria*) with alcohol, acetic acid and water, are now made with hydro-acetic acid.

### FLUIDEXTRACTUM BERBERIDIS.

#### Fluidextract of Berberis.

Prepared from *Berberis* (q. v.).

**Dose.**—"Average dose: 2 Cc. (30 minims)." (U. S. P.)

### FLUIDEXTRACTUM EUONYMI.

#### Fluidextract of Euonymus.

The solid extract of *Euonymus*, which was already official, is now prepared from this fluidextract.

**Dose.**—"Average dose: 0.5 Cc. (8 minims)." (U. S. P.)

### FLUIDEXTRACTUM GRANATI.

#### Fluidextract of Pomegranate.

Hitherto only the bark of the stem and root of *Granatum* (*Pomegranate*) has been official; it was often administered in the form of a decoction (official in the Br. P.), but this was very unpleasant to take, owing to the large amount of tannic acid present. A mixture of the tannates of the most important active constituents (four alkaloids) of *Granatum* has also been introduced under the name *Pelletierinæ Tannas* (q. v.).

**Dose.**—"Average dose: 2 Cc. (30 minims)." (U. S. P.)

### FLUIDEXTRACTUM QUERCUS.

#### Fluidextract of Quercus.

Prepared from the official *Quercus* (*Quercus Alba*, U. S. P., 1890), the bark of the white oak. The medicinal properties depend upon the tannin contained in the bark.

**Dose.**—"Average dose: 1 Cc. (15 minims)." (U. S. P.)

### FLUIDEXTRACTUM QUILLAJE.

#### Fluidextract of Quillaja.

The tincture of *Quillaja* (soapbark) was already official.

It has sometimes been proposed to use *quillaja* or one of its most important constituents (saponin) as an emulsifying agent for cod-liver

oil, etc.; in the present state of our knowledge such use would seem to be unjustifiable (see Keirle and Dunning, Proc. Amer. Pharm. Assoc., 52, p. 402).

**Dose.**—"Average dose: 0.2 Cc. (3 minims)." (U. S. P.)

This fluidextract is contained in the National Formulary.

### FLUIDEXTRACTUM RHAMNI PURSHIANÆ AROMATICUM.

#### Aromatic Fluidextract of Cascara Sagrada.

This is the Aromatic Fluidextract of Cascara Sagrada of the National Formulary. It differs from the Fluidextract, which was already official, in having an aromatic flavor and being devoid of the intensely bitter principle occurring in the bark. It might well take the place of a number of commercial articles. The Extractum Rhamni Purshianæ (q. v.) is also a new introduction.

**Dose.**—"Average dose: 1 Cc. (15 minims)." (U. S. P.)

### FLUIDEXTRACTUM SCOPOLE.

#### Fluidextract of Scopola.

Prepared from Scopola (q. v.) and containing 0.5 per cent of the mydriatic alkaloids of this drug. A method of assay is given in the U. S. Pharmacopœia.

**Dose.**—"Average dose: 0.05 Cc. (1 minim)." (U. S. P.)

This dose contains 0.00025 gram ( $\frac{1}{2000}$  grain) of the scopola alkaloids.

### FLUIDEXTRACTUM STAPHISAGRIÆ.

#### Fluidextract of Staphisagria.

Prepared from the seeds, the official part, of *Delphinium staphisagria* (Stavesacre). Several bases have been described as occurring in stavesacre, but they may all be decomposition products of the aconitine-like alkaloid, delphinine.

**Dose.**—"Average dose: 0.05 Cc. (1 minim)." (U. S. P.)

### FLUIDEXTRACTUM SUMBUL.

#### Fluidextract of Sumbul.

This and the Extract of Sumbul (q. v.) are new additions, while the tincture (U. S. P., 1890) is dropped.

**Dose.**—"Average dose: 2 Cc. (30 minims)." (U. S. P.)

### GAMBIR.

#### Gambir.

This takes the place of Catechu of the Pharmacopœia of 1890. Catechu is an extract prepared from the wood of *Acacia catechu* (natural order Leguminosæ); Gambir is an extract prepared from the leaves

and twigs of *Uncaria gambir* (fam. Rubiaceæ.). Both drugs contain a large percentage of tannic acid and its compounds. Gambir was introduced on account of the difficulty of obtaining in the market true *Acacia catechu*. The *Tinctura Catechu Composita* and the *Trochisci Catechu* (U. S. P., 1890) are replaced by *Tinctura Gambir Composita* and *Trochisci Gambir*.

**Dose.**—"Average dose: 1 Gm. (15 grains)." (U. S. P.)

### GELATINUM.

#### Gelatin.

Official in the British Pharmacopœia under the same name; in the German as *Gelatina alba*. The U. S. Pharmacopœia demands that upon ignition it leave not more than 2 per cent of ash. Most of the gelatin on the market has an acid reaction.

### GELATINUM GLYCERINATUM.

#### Glycerinated Gelatin.

A mixture of equal parts of gelatin and glycerin. The mass when cold is solid, but easily melts on applying gentle heat.

Basis for suppositories and bougies.

Of late years both ointments and cerates have been largely superseded, especially in Europe, by dermatologic pastes and glycerogelatin. The former are mixtures of the medicinal agents with starch, dextrin, or kaolin, and glycerin, soft soap, petrolatum, or lard, and are intended chiefly for antiseptic, astringent, or germicidal effects. The glycerogelatin are firmer than the pastes, and must be melted before they can be applied.

### GLANDULE SUPRARENALES SICCE.

#### Desiccated Suprarenal Glands.

The cleaned, dried, and powdered suprarenal glands of the sheep or ox, freed from fat.

**Properties.**—A light, yellowish, amorphous powder, having a slight characteristic odor; partially soluble in water. One part of the dried glands represents approximately 6 parts of fresh glands.

Aqueous extracts of the glands rapidly deteriorate on keeping and should, therefore, be freshly prepared.

**Dose.**—"Average dose: 0.250 Gm.=250 milligrammes (4 grains)." (U. S. P.)

The blood-pressure raising constituent of the suprarenal glands is upon the market under the names *adnephryn*, *adrenaline*, *epinephrine*, *epirenan*, *hemisine*, *paranephryn*, *suprarenalin*, *suprarenin*, etc.



## GLANDULE THYROIDEÆ SICCÆ.

## Desiccated Thyroid Glands.

The cleaned, dried, and powdered thyroid glands of the sheep, freed from fat.

A liquid preparation is official in the British Pharmacopœia.

**Properties.**—A yellowish amorphous powder, having a slight peculiar odor; partially soluble in water.

**Dose.**—“Average dose: 0.250 Gm.=250 milligrammes (4 grains).” (U. S. P.)

Numerous extracts of the thyroid are upon the market, many of them purporting to be the active constituent. *Aiodine*, *opothyroidine*, and *thyroglandine* are other preparations on the market.

*Thyreoidectin* and *rodagen* represent a new series of preparations quite recently introduced which must not be confused with the above: their action is stated to be exactly the opposite of that of the thyroid preparations. *Thyreoidectin* is prepared from the blood, *rodagen* from the milk, of animals from which the thyroids have been removed.

## GLYCERITUM FERRI, QUININÆ ET STRYCHNINÆ PHOSPHATUM.

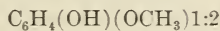
## Glycerite of the Phosphates of Iron, Quinine and Strychnine.

This preparation is a concentrated form of one of the popular and useful combinations of tonics which might well replace some of the many commercial articles; it is prepared according to a fixed and definite formula (see U. S. P.), whereas the latter class are made according to the special formulæ of the different manufacturers. (See also Elixir Ferri, Quininæ et Strychninæ Phosphatum.) This glycerite is a stable solution which may be kept in stock, and from which the Syrup of the Phosphates of Iron, Quinine and Strychnine may readily be prepared.

**Dose.**—“Average dose: 1 Cc. (15 minims).” (U. S. P.) 1 Cc. contains 0.080 Gm.=80 milligrammes ( $1\frac{1}{4}$  grains) of soluble ferric phosphate, 0.104 Gm.=104 milligrammes ( $1\frac{3}{5}$  grains) of quinine, and 0.0008 Gm.=0.8 milligrammes ( $\frac{1}{50}$  grain) of strychnine. The ratio of quinine to strychnine is four times as great in the glycerite as in the elixir.

## GUAIACOL.

## Guaiacol.



One of the chief constituents of creosote: prepared either from beechwood tar, or synthetically. Chemically it is the monomethyl ether of pyrocatechin (orthodihydroxy-benzene).

**Character.**—Either a clear, colorless or light yellow, oily fluid, or colorless, prismatic crystals, which melt at 28.5° C. It has an agreeable, aromatic odor.

**Solubility.**—Soluble in water (1:53), glycerin (1:1), and easily in alcohol. Being phenolic in character, it readily dissolves in caustic alkalies and forms salts with a large number of acids, one of which (the carbonate) has been made official.

Of late years creosote has been largely superseded by guaiacol, upon which the value of creosote no doubt depends.

**Dose.**—“Average dose: 0.5 Cc. (8 minims).” (U. S. P.)

**Caution.**—It should be preserved in dark, amber-colored bottles, protected from the light. Guaiacol which has become dark from exposure to light may be rendered colorless by redistillation. To be used cautiously with other drugs of similar physiologic action, e. g., Creosotum, Resorcinol, Phenylis Salicylas, etc.

### GUAIACOLIS CARBONAS.

Guaiacol Carbonate.



A guaiacol derivative obtained by the action of carbonyl chloride upon sodium-guaiacolate.

Also known as *duotal*.

**Character.**—A white, crystalline, neutral powder, nearly odorless and tasteless.

**Solubility.**—Insoluble in water; soluble in cold (1:48), more so in hot, alcohol; slightly soluble in glycerin and fatty oils.

**Dose.**—“Average dose: 1 Gm. (15 grains).” (U. S. P.)

**Other Guaiacol Compounds.**—Numerous combinations of guaiacol with other acids, etc., are in the market, such as the benzoate (*benzosol*), benzyl-guaiacol, cacodylate (*cacodyliacol*), cinnamate (*styracol*), phosphate, salicylate (*guaiacol-salol*), sulphonate, valerianate (*geosot*), etc.

### HAMAMELIDIS CORTEX.

Hamamelis Bark.

Both the bark and twigs, and the leaves of *Hamamelis virginiana* are now recognized by the Pharmacopœia; the former are introduced under the above title and the old Hamamelis (U. S. P., 1890) becomes Hamameiidis Folia.

**Dose.**—“Average dose: 2 Gm. (30 grains).” (U. S. P.)

### HEXAMETHYLENAMINA.

Hexamethylenamine.



A condensation product of formaldehyde and ammonia. Chemically it is hexamethylene-tetramine. Also known as *aminoform*, *ammonio-formaldehyde*, *cystamine*, *cystogen*, *formin*, *uritone*, and *urotropin*.

**Character.**—Colorless, lustrous, odorless crystals, having a sweetish, then somewhat bitter, taste. Its aqueous solution has an alkaline reaction to litmus.

**Solubility.**—Easily soluble in water (1:1.5), less so in alcohol (1:10).

In solution it is decomposed by dilute sulphuric acid with liberation of formaldehyde; it is precipitated by tannic acid and mercuric chloride.

**Dose.**—“Average dose: 0.250 Gm. = 250 milligrammes (± grains).” (U. S. P.)

**Caution.**—It should be kept in well-stoppered bottles.

**Allied Compounds.**—Hexamethylene-tetramine readily forms compounds with a large number of substances; among those suggested for use in medicine the following may be mentioned:

Hexamethylenamine salicylate, *urotropin salicylate*, or *saliformin*; a colorless, crystalline powder of nauseous, sweetish, astringent taste.

Hexamethylenamine-ethylbromide, *bromalin*, or *bromoformin*; a colorless, crystalline powder of a sweetish saline taste.

Hexamethylenamine-tannin, *tannopin*, or *tannon*; a brown tasteless powder, nearly insoluble in water and alcohol.

Dioxybenzol-hexamethylenamine, *hetralin*, contains 60 per cent of hexamethylenamine.

*Chinotropin* and *chinfoformin* are quinates of hexamethylenamine.

*Helmitol* is a recently introduced compound of hexamethylenamine with anhydromethylene citric acid. *Citarin* (sodium anhydromethylene citrate) is another compound from which formaldehyde is split off in the organism.

## HOMATROPINÆ HYDROBROMIDUM.

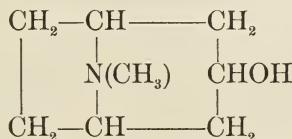
### Homatropine Hydrobromide.



Official under the same name in the British Pharmacopœia; as Homatropinum hydrobromicum in the German and Swiss Pharmacopœias.

“The hydrobromide of an alkaloid obtained by the condensation of tropine and mandelic acid.”

**Chemistry.**—Atropine may be broken up, by the action of alkalies, into an alkaloid, tropine, and an aromatic acid, tropic acid. Tropine is a pyridine derivative having the structural formula



Tropine forms ester-like compounds with many acids; the compounds with aromatic acids are called tropeins. Homatropine is one of these tropeins; as stated above, it is formed by the union of tropine and mandelic acid; the latter is phenylglycollic acid ( $C_6H_5CH < \begin{smallmatrix} OH \\ COOH \end{smallmatrix}$ ).

Tropic acid (the acid of atropine) is phenylhydraerylic acid ( $C_6H_5CH < \begin{matrix} CH_2OH \\ COOH \end{matrix}$ ). Scopolamine (hyoscine) is formed by the union of tropic acid with scopoline, a compound similar to tropine.

**Properties.**—Small, colorless, odorless, rhombic crystals or crystalline powder, having a bitter taste. Soluble in 5.7 parts of water and 32.5 parts of alcohol. It should be kept in well-stoppered vials protected from light.

**Dose.**—“Average dose: 0.0005 Gm. = 0.5 milligramme ( $\frac{1}{288}$  grain).” (U. S. P.)

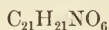
The physiological action of homatropine is similar to that of atropine, but it is less poisonous. The mydriatic effects of homatropine appear more quickly and pass off in a shorter time than do those of atropine.

The hydrochloride, sulphate, and salicylate of homatropine have been used, but they seem to have no advantage over the hydrobromide.

*Euphthalmin* is a recently introduced mydriatic, having a physiological action very similar to homatropine; it is a mandelic acid derivative of *beta-eucaine*.

#### HYDRASTINA.

##### Hydrastine.



An alkaloid obtained from Hydrastis. The U. S. Pharmacopœia, Eighth Decennial Revision, demands that Hydrastis contain not less than 2.5 per cent of Hydrastine. Hydrastis contains also the alkaloids berberine to the extent of 3.5 to 5 per cent, and canadine, but its physiological action is due largely to the Hydrastine. Hydrastine is frequently called in commerce the “white alkaloid of hydrastis.”

The alkaloid hydrastinine (the hydrochloride of which is official) is obtained from Hydrastine by the action of oxidizing agents. The alkaloid Hydrastine should not be confused with the mixture of hydrastine, berberine, etc., sold under the same name.

**Properties.**—“White, to creamy white, glistening prisms, sometimes of large size, possessing a bitter taste, and permanent in the air.” Almost insoluble in water; soluble in 135 parts of alcohol.

“If a crystal of Hydrastine be dissolved in diluted sulphuric acid and a solution of potassium permanganate (1 in 10) be added, a blue fluorescence will be developed (distinction from hydrastinine).”

**Dose.**—“Average dose: 0.010 Gm. = 10 milligrammes ( $\frac{1}{5}$  grain).” (U. S. P.)

Hydrastine is extensively used in preparing the so-called “colorless hydrastis,” which is a solution of the alkaloid, in a mixture of water and glycerin, with the aid of hydrochloric or sulphuric acid.



## IODOLUM.

Iodol.

 $C_4I_4NH$ 

Tetraiodopyrrol, a derivative of the base pyrrol ( $C_4H_5N$ ) obtained by the direct action of iodine upon the base in the presence of alcohol.

**Properties.**—A light, grayish-brown, crystalline powder without odor or taste. Very slightly soluble in water (1:4900), much more so in alcohol (1:9); soluble in fixed oils.

**Dose.**—“Average dose: 0.250 Gm.=250 milligrammes (4 grains).” (U. S. P.)

This is one of the vast number of compounds proposed in the last few years as substitutes for iodoform. The iodine of iodol is apparently less easily split off the molecule than that of iodoform, and it is said to be less liable to produce poisoning.

**Other iodine compounds.**—Among the enormous number of other iodine compounds proposed as substitutes for iodoform may be mentioned: Thymolis Iodidum (U. S. P., Eighth Decennial Revision, commonly known as *aristol*); *airol* (bismuth oxy-iodo-gallate, with 20 per cent of iodine); *sanoform* (diiodo-methylsalicylate); the potassium, sodium, mercury, and zinc salts of *soziodolic acid* (phenol-sulphonic acid in which two atoms of hydrogen have been substituted by two atoms of iodine— $C_6H_2I_2 < \begin{matrix} (OH) \\ SO_2 \\ OH \end{matrix} \right)$ , known as *soziodolates*; *nosophen*, *antinosine*, and *eudoxine* (all iodine compounds of phenolphthalein); *losophan* and *europfen* (combinations of cresol and iodine); *loretin* and *vioform* (derivatives of quinoline containing iodine); *diiodoform* (tetraiodoethylene,  $C_2I_4$ ); sodium diiodosalicylate; acetone iodide; iodoso-benzoic acid, etc.

Various mixtures of iodoform and other substances have been made with the object of concealing the odor of the former; thus, *eka-iodoform* is said to consist of iodoform and paraformaldehyde; *anozol* of iodoform and thymol; *iodoformin* of iodoform and hexamethylene tetramine, etc. *Iodoformogen* is a proteid compound of iodoform. Iodoformum Aromaticum, N. F., is a mixture of iodoform and coumarin.

## KAOLINUM.

Kaolin.

Official in the British Pharmacopœia under same name. A native aluminum silicate, consisting largely of the pure silicate  $H_2Al_2Si_2O_8 + H_2O$ . It is a very pure clay.

**Properties.**—Soft, white or yellowish-white powder, odorless, and having an earthy or clay-like taste.

Insoluble in water.

Kaolin is contained in Cataplasma Kaolini (q. v.). It is used in dusting powders; also in pills containing easily reduced bodies, such as silver nitrate or potassium permanganate, which can not be mixed with ordinary excipients.

### LIQUOR ANTISEPTICUS.

#### Antiseptic Solution.

A solution of mild aromatics and antiseptics similar to certain commercial preparations. Among other things it contains about 2 per cent of boric acid, 0.1 per cent each of benzoic acid and thymol, and 25 per cent of alcohol.

**Dose.**—“Average dose: 4 Cc. (1 fluidrachm).” (U. S. P.)

### LIQUOR CHLORI COMPOSITUS.

#### Compound Solution of Chlorine.

#### Chlorine Water.

This takes the place of Aqua Chlori (U. S. P., 1890). The method of preparation (for which see the Pharmacopœia) is materially changed and simplified. When freshly prepared it contains about 0.4 per cent of chlorine with some oxides of chlorine and potassium chloride.

**Dose.**—“Average dose: 4 Cc. (1 fluidrachm).” (U. S. P.)

### LIQUOR CRESOLIS COMPOSITUS.

#### Compound Solution of Cresol.

Liquor Cresoli saponatus is the official German title of a somewhat similar preparation. It is essentially a linseed-oil-soap solution of cresol, of 50 per cent strength; the soap dissolves the cresol as do alkalis. This is a mixture of much more definite composition than many commercial preparations of similar nature.

For practical use the 50 per cent solution is diluted with water to various degrees according to need.

Other preparations of this nature are known as *creolin*, *disinfectol*, *enterocresol*, *germol*, *cresolin*, *lysol*, *lysitol*, etc. (See Cresol).

### LIQUOR FORMALDEHYDI.

#### Solution of Formaldehyde.

An aqueous solution containing not less than 37 per cent by weight of absolute Formaldehyde (H.CO<sub>2</sub>H); an assay process is provided. Official in the German Pharmacopœia as Formaldehydum solum and variously known as *formalin*, *formol*, *methylaldehyde*, *oxymethylene*, *methanal*, etc.

**Properties.**—Formaldehyde itself is a gas at ordinary temperatures having a very pungent odor. The various products on the market are solutions of the gas in water. Formaldehyde readily undergoes a

molecular change called polymerization, whereby a solid form is obtained, known as paraformaldehyde or simply *paraform*. When a solution of formaldehyde is evaporated by heat, and more slowly by long standing, paraformaldehyde separates as a white, flocculent, nearly odorless mass, which is almost insoluble in water, alcohol, or ether, and which begins to sublime below 100° C. When heated, paraformaldehyde vaporizes and reforms the gaseous formaldehyde. It occurs in the market in tablets which are employed for disinfecting purposes.

Formaldehyde is very active chemically; it has a strong reducing action on silver, copper, and mercury salts, and unites readily with ammonia, forming the official odorless Hexamethylenamine (which see). It is easily oxidized by hydrogen dioxide and potassium permanganate, especially in alkaline solution.

Several dusting powders containing formaldehyde, in combination, have been introduced; thus, *glutol* is a compound of gelatin and formaldehyde, *amyliform*, of starch and formaldehyde, etc.

Formaldehyde is a constituent of many food preservatives, embalming preparations, etc.

**Caution.**—Keep well stoppered in a moderately cool place and protected from light.

#### LIQUOR SODII PHOSPHATIS COMPOSITUS.

Compound Solution of Sodium Phosphate.

A fairly stable concentrated solution containing 1 Gm. of Sodium Phosphate in each Cc.

**Dose.**—“Average dose: 8 Cc. (2 fluidrachms).” (U. S. P.)

Keep well stoppered and moderately warm.

#### MAGNESII SULPHAS EFFERVESCENS.

Effervescent Magnesium Sulphate.

A similar compound is official under the same name in the British Pharmacopœia; known also as effervescent Epsom salt, and as *magnesii sulphas granulatus*.

This may take the place of *Magnesii Citras Effervescens* (U. S. P., 1890), which has been dropped.

**Dose.**—“Average dose: 16 Gm. (240 grains).” (U. S. P.)

#### MALTUM.

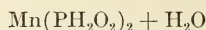
Malt.

This is a reintroduction; Maltum was official in the U. S. Pharmacopœia, 1880, but was dropped in 1890. Used for the preparation of *Extractum Malti* (q. v.).

**MANGANI DIOXIDUM PRÆCIPITATUM.****Precipitated Manganese Dioxide.**

To replace Mangani Dioxidum, U. S. Pharmacopœia, 1890. It consists chiefly of manganese dioxide ( $MnO_2$ ), with small amounts of other oxides of manganese, corresponding to not less than 80 per cent of manganese dioxide. The Mangani Dioxidum (1890) was the native crude manganese dioxide and was only required to contain at least 66 per cent of the pure dioxide.

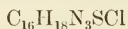
**Dose.**—“Average dose: 0.250 Gm. = 250 milligrammes (4 grains).” (U. S. P.)

**MANGANI HYPOPHOSPHIS.****Manganese Hypophosphite.**

It should contain not less than 97 per cent of pure manganese hypophosphite.

**Dose.**—“Average dose: 0.200 Gm. = 200 milligrammes (3 grains).” (U. S. P.)

It is contained in Syrupus Hypophosphitum Compositus.

**METHYLTHIONINE HYDROCHLORIDUM.****Methylthionine Hydrochloride.****Methylene Blue.**

Chemically, it is tetramethylthionine hydrochloride.

**Properties.**—Dark, green, crystalline powder, or prismatic crystals having a bronze-like luster.

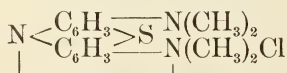
Readily soluble in water, somewhat less so in alcohol; the solutions are of a deep blue color.

Incompatible with potassium iodide. Reducing agents decolorize it.

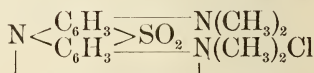
**Dose.**—“Average dose: 0.250 Gm. = 250 milligrammes (4 grains).” (U. S. P.)

**Caution.**—Not to be confounded with commercial methylene blue, which is often the zinc chloride double salt of tetramethylthionine, is employed as a dye or stain, and is unfit for internal administration.

Methylene azure, a dye which has recently come into prominence as a stain in histology (Romanowsky's stain, for example, depends upon the methylene azure present in “ripened” methylene blue), is derived from methylene blue by the addition of two atoms of oxygen to the sulphur.



Methylene blue



Methylene azure (chloride)



Methylene azure is almost always present in even the best specimens of methylene blue. It may be detected by adding ammonia to a solution of methylene blue and then shaking with ether; the methylene azure passes into the ether, which is colored red.

### OLEATA.

#### Oleates.

Three new oleates have been introduced and one (*Oleatum Zinci*, U. S. P., 1890) dropped.

For method of preparation see the *Pharmacopœia*.

The oleate of quinine is also in the National Formulary; other (unofficial) oleates in the National Formulary are: oleate of aconitine, lead oleate, and zinc oleate (different from the U. S. P. 1890 Oleate of Zinc).

#### OLEATUM ATROPINE.

##### Oleate of Atropine.

Containing 2 per cent of atropine.

#### OLEATUM COCAINE.

##### Oleate of Cocaine.

Containing 5 per cent of cocaine.

#### OLEATUM QUININE.

##### Oleate of Quinine.

Containing 25 per cent of quinine.

#### OPIUM GRANULATUM.

##### Granulated Opium.

Opium dried at a temperature not exceeding 85° C. and reduced to a coarse (No. 20) powder; *Opii Pulvis* is prepared similarly, but it is reduced to a very fine powder; the *Pharmacopœia* requires that it contain not less than 12 per cent nor more than 12.5 per cent of crystallized morphine when assayed by the pharmacopœial process; the powdered and deodorized opium are also required to contain this percentage of crystallized morphine.

The Tincture of Opium is now made from granulated opium instead of from powdered opium, as in the U. S. *Pharmacopœia*, 1890. Much of the tincture of opium on the market seems to be under strength; it is hoped that a more uniform product will be obtained by the use of granulated opium.

**Dose.**—“Average dose: 0.065 Gm. = 65 milligrammes (1 grain).” (U. S. P.)

**PARAFFINUM.****Paraffin.**

A mixture of solid hydrocarbons, chiefly of the methane series. The paraffin of the U. S. Pharmacopœia melts between  $51.6^{\circ}$  and  $57.2^{\circ}$  C. The "hard paraffin" (Paraffinum Durum) of the British Pharmacopœia melts between  $54.4^{\circ}$  and  $57.2^{\circ}$  C., while the "Paraffinum solidum" of the German Pharmacopœia melts between  $74^{\circ}$  and  $80^{\circ}$  C.

**PELLETIERINE TANNAS.****Pelletierine Tannate.**

"A mixture in varying proportions of the tannates of four alkaloids (punicine, iso-punicine, methyl-punicine, and pseudo-punicine) obtained from *Punica granatum*" (Pomegranate). Also known as punicinum tannicum. The alkaloids are also known as pelletierine, iso-pelletierine, etc.

**Character.**—A yellowish-white, odorless, amorphous powder, having an astringent taste, and a weak acid reaction.

**Solubility.**—Soluble in water (1:235), alcohol (1:12.6), and in warm dilute acids.

**Dose.**—"Average dose: 0.250 Gm. = 250 milligrammes ( $\frac{4}{10}$  grains)." (U. S. P.)

The pelletierines of commerce seem to vary greatly; some are ten times as poisonous as others. While the U. S. Pharmacopœia names, as the average dose of the tannate, 0.25 Gm., some writers recommend 0.75 to 1.5 Gm. Very unpleasant effects are said to have resulted from 0.4 to 0.5 Gm.

**PETROLATUM ALBUM.****White Petrolatum.**

"A white unctuous mass of about the consistency of an ointment." It is purified petrolatum and is used in the preparation of the Ointment of Boric Acid, the Ointment of Phenol (Unguentum Acidi Carbolici, U. S. P., 1890), etc.

**PHENOL LIQUEFACTUM.****Liquefied Phenol.**

Practically the Acidum Carbolicum Liquefactum of the British and German Pharmacopœias. It is prepared from Phenol (Acidum Carbolicum, U. S. P., 1890) by the addition of distilled water in the proportion of 1 Gm. of the latter to 9 Gm. of Phenol. The U. S. Pharmacopœia Phenol must contain not less than 96 per cent of absolute phenol; whereas this preparation, Phenol Liquefactum, contains not less than 86.4 per cent, by weight, of absolute phenol and about 13.6

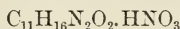
per cent, by weight, of water. Introduced on account of the ease of dispensing.

1 Gm. of Phenol (U. S. P.) equals about 1.11 Gm. of Liquefied Phenol, or 1 Gm. Liquefied Phenol equals about 0.9 Gm. of Phenol.

**Dose.**—“Average dose: 0.05 Cc. (1 minim).” (U. S. P.)

### PILOCARPINE NITRAS.

•Pilocarpine Nitrate.



This is the only salt of pilocarpine official in the British Pharmacopœia. The revised U. S. Pharmacopœia contains two salts of pilocarpine; the Pilocarpinæ Hydrochloras (U. S. P., 1890) is retained under the name of Pilocarpinæ Hydrochloridum, and the nitrate is introduced.

**Character.**—Colorless, or white, shining crystals, odorless, and having a faintly bitter taste. It is permanent in the air, whereas the hydrochloride is deliquescent on exposure to the air.

**Solubility.**—Soluble in water (1:4), alcohol (1:60), in warm alcohol (1:16). The aqueous solution (1 in 100) is acid to litmus.

**Dose.**—“Average dose: 0.010 Gm.=10 milligrammes ( $\frac{1}{5}$  grain).” (U. S. P.)

### PILULÆ LAXATIVÆ COMPOSITE.

Compound Laxative Pills.

An official preparation which may well replace a number of similar commercial articles.

Each pill contains 0.013 Gm. = 13 milligrammes ( $\frac{1}{5}$  grain) Aloin, 0.0005 Gm. = 0.5 milligramme ( $\frac{1}{200}$  grain) Strychnine, 0.008 Gm. = 8 milligrammes ( $\frac{1}{8}$  grain) Extract of Belladonna Leaves, and 0.004 Gm. = 4 milligrammes ( $\frac{1}{25}$  grain) of Ipecac.

**Dose.**—“Average dose: 2 pills.” (U. S. P.)

Pilulæ Aloini, Strychninæ et Belladonnæ, N. F., contain, with the exception of the Ipecac, the same active ingredients and in the same proportions.

### PILULÆ PODOPHYLLI, BELLADONNÆ ET CAPSICI.

Pills of Podophyllum, Belladonna and Capsicum.

Each pill contains 0.016 Gm. = 16 milligrammes ( $\frac{1}{4}$  grain) Resin of Podophyllum, 0.008 Gm. = 8 milligrammes ( $\frac{1}{8}$  grain) Extract of Belladonna Leaves, and 0.032 Gm. = 32 milligrammes ( $\frac{1}{2}$  grain) Capsicum.

**Dose.**—“Average dose: 1 pill.” (U. S. P.)

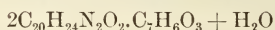
The same pill is included in the National Formulary under the same name.

**PULVIS ACETANILIDI COMPOSITUS.****Compound Acetanilide Powder.**

A mixture of Acetanilide, Caffeine, and Sodium Bicarbonate; it is a modification of the National Formulary article of the same name and has been known as Acetanilid Compound (Aulde). The sodium bicarbonate increases the solubility of the acetanilide.

**Dose.**—"Average dose: 0.500 Gm. = 500 milligrammes (7½ grains)." (U. S. P.)

Acetanilide is the cheapest of the common antipyretics and it is extensively used in the "headache powders" sold under such a variety of names. These powders frequently contain also caffeine and an alkaline salt, usually sodium bicarbonate or ammonium carbonate. (For analyses of a number of these powders see Jour. Amer. Med. Assoc., Vol. 44, p. 1790, 1905.)

**QUININE SALICYLAS.****Quinine Salicylate.**

**Character.**—Colorless needles, permanent in air, but acquiring a pinkish tinge after a time.

**Solubility.**—Soluble in cold water (1:77), somewhat more so in warm (1:35), in alcohol (1:11), and in glycerin (1:16).

It contains 68.79 per cent Quinine (the Bisulphate contains 59.1 per cent Quinine, the Hydrobromide 76.6 per cent, the Hydrochloride 81.8 per cent, the Sulphate 74.3 per cent). The Bisulphate is soluble in 8.5 parts of water, the Hydrobromide in 40 parts, the Hydrochloride in 18 parts, the Sulphate in 720 parts; the official alkaloid (containing 3 molecules of water) is soluble in 1,550 parts of water.

**Dose.**—"Average dose: 0.250 Gm. = 250 milligrammes (4 grains)." (U. S. P.)

**SABAL.****Sabal.**

The partially dried ripe fruit of *Serenoa serrulata*, commonly known as saw palmetto.

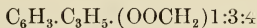
Not much is known concerning the active principles of this drug, and there seems to have been no satisfactory investigation of its physiological action. Coblenz found in the pulp of the berries a volatile oil, a fixed oil, a fat, an alkaloid, a resin, dextrin, and glucose.

**Dose.**—"Average dose: 1 Gm. (15 grains)." (U. S. P.)



## SAFROLUM.

## Safrol.



“The methylene ether of allyl pyrocatechol, found in oil of sassafras, camphor oil,” etc.

**Properties.**—A colorless, or faintly yellow, liquid with a sassafras-like odor. Soluble in about its own volume of strong alcohol and in about 30 volumes of 70 per cent alcohol.

Safrol is contained to the extent of 80 per cent in the official oil of sassafras (*Oleum Sassafras*). Much of the safrol of commerce is obtained from camphor oil. Safrol is used to a considerable extent in flavoring drinks (sarsaparilla waters) and perfuming soaps. Heffter (*Arch. f. exp. Path. u. Pharm.*, 35, p. 354) considers safrol to be the most poisonous of the volatile oils, and thinks its widespread use not unattended with danger. The effects of chronic poisoning are similar to those of yellow phosphorus.

**Dose.**—“Average dose: 0.3 Cc. (5 minims).” (U. S. P.)

## SCOPOLA.

## Scopola.

The dried rhizome of *Scopola carniolica*, Jacquin (Fam. *Solanaceæ*). Scopola is closely related to Belladonna and Hyoscyamus.

The Pharmacopœia demands that the drug contain not less than 0.5 per cent of alkaloids; it is assayed by the same process as are belladonna leaves.

Preparations admitted into the U. S. Pharmacopœia, Eighth Decennial Revision: Extract of Scopola and Fluidextract of Scopola (q. v.)

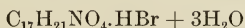
**Dose.**—“Average dose: 0.045 Gm. = 45 milligrammes ( $\frac{3}{4}$  grain).” (U. S. P.)

The alkaloid of Scopola is almost wholly hyoscyamine. The content of the alkaloids in Scopola is remarkably uniform (about 0.55 per cent), whereas the percentage of alkaloids in Belladonna varies from 0.2 to above 1 per cent.

There has been much discussion as to how far Scopola can replace Belladonna in therapeutics; its preparations are said to be used extensively in the manufacture of “belladonna plasters.”

## SCOPOLAMINÆ HYDROBROMIDUM.

## Scopolamine Hydrobromide.



“The hydrobromide of an alkaloid obtained from plants of the *Solanaceæ*; chemically identical with Hyoscyine Hydrobromide.”

Although Hyoscyine Hydrobromide, which was admitted into the U. S. Pharmacopœia, 1890, and Scopolamine Hydrobromide are iden-

tical, both names are used in the U. S. Pharmacopœia, Eighth Decennial Revision, as separate headings, because most people are familiar with the name Hyoscine but not with Scopolamine. Scopolamine is formed by the union of tropic acid with scopoline, a compound similar to tropine. (See Homatropine.)

In the British Pharmacopœia Scopolamine Hydrobromide is used as a synonym for Hyoscine Hydrobromide; in the German Pharmacopœia only the name Scopolaminum hydrobromicum is retained.

**Dose.**—"Average dose: 0.0005 Gm. = 0.5 milligramme ( $\frac{1}{128}$  grain)." (U. S. P.)

### SERUM ANTIDIPHThERICUM.

Antidiphtheric Serum.

Diphtheria Antitoxin.

"A fluid separated from the coagulated blood of a horse immunized through the inoculation of diphtheric toxin."—U. S. Pharmacopœia. The German Pharmacopœia recognizes also the dried serum.

Antidiphtheric serum gradually loses its power, the loss in one year varying between 10 and 30 per cent.

"The standard of strength, expressed in units of antitoxic power, should be that approved or established by the U. S. Public Health and Marine-Hospital Service." (U. S. P.) All manufacturers selling diphtheria antitoxin in the District of Columbia, or in States other than the one in which it is manufactured, must secure a license issued by the Secretary of the Treasury on recommendation of the Surgeon-General of the Public Health and Marine-Hospital Service. (For a full discussion of the official standard, see Rosenau, M. J.: The immunity unit for standardizing diphtheria antitoxin, Bulletin No. 21, Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service, 1905.)

**Dose.**—"Average dose: 3,000 units. Immunizing dose for well persons: 500 units." (U. S. P.)

**Caution.**—Should be kept in sealed glass containers in a dark place at temperatures between  $4.5^{\circ}$  and  $15^{\circ}$  C. ( $40^{\circ}$  and  $59^{\circ}$  F.).

### SODII ARSENAS EXSICCATUS.

Exsiccated Sodium Arsenate.



This is the same as the Sodii Arsenas of the British Pharmacopœia; also known as anhydrous sodium arsenate.

**Properties.**—An amorphous, odorless, white powder. Permanent in dry air. Soluble in 3 parts of water; very soluble in boiling water.

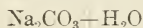
This is prepared from Sodium Arsenate (already official) by expelling by heat the seven molecules of water of the latter. The hydrous sodium arsenate (Sodii Arsenas, U. S. P.) is efflorescent in dry air

and somewhat deliquescent in moist air; hence the percentage of arsenic is somewhat uncertain. The new preparation is permanent in dry air. The hydrous sodium arsenate contains 40.4 per cent of water; hence, a given weight of this substance will contain but little more than half as much arsenic as an equal weight of the exsiccated. The average dose of the latter is accordingly placed at about one-half that of the former.

**Dose.**—“Average dose: 0.003 Gm. = 3 milligrammes ( $\frac{1}{30}$  grain).” (U. S. P.)

### SODII CARBONAS MONOHYDRATUS.

Monohydrated Sodium Carbonate.



Sodii Carbonas and Sodii Carbonas Exsiccatus (U. S. P., 1890) are dismissed from the Pharmacopœia and the monohydrated salt introduced.

The Sodii Carbonas contained ten molecules of water of crystallization or 63 per cent; part of this was lost on exposure to air, so that the salt was of uncertain strength. The Sodii Carbonas Exsiccatus contained about 26 per cent of water and probably corresponded to the formula  $\text{Na}_2\text{CO}_3 + 2\text{H}_2\text{O}$ . This salt was somewhat hygroscopic. The monohydrated salt does not effloresce at ordinary temperatures, nor does it absorb much moisture. It is therefore more uniform in composition than either of the others.

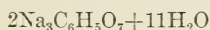
**Character.**—A white, crystalline, granular powder, odorless and having a strong alkaline taste. It is somewhat less soluble than Sodii Carbonas (U. S. P., 1890), but more so than Sodii Bicarbonas.

**Solubility.**—Soluble in water (1:2.9), in boiling water (1:1.8), in glycerin (1:8); insoluble in alcohol.

**Dose.**—“Average dose: 0.250 Gm. = 250 milligrammes (4 grains).” (U. S. P.)

### SODII CITRAS.

Sodium Citrate.



**Properties.**—A white, granular powder, odorless. It slowly effloresces on exposure to dry air. Soluble in 1.1 parts of cold water and in 0.4 part of boiling water; slightly soluble in alcohol.

**Dose.**—“Average dose: 1 Gm. (15 grains).” (U. S. P.)

A carbonated solution of Sodium Citrate is contained in the National Formulary under the name of Liquor Sodii Citratis and in the German Pharmacopœia under the name Potio Riveri.

**SODII PHOSPHAS EFFERVESCENS.****Effervescent Sodium Phosphate.**

A similar compound is official under the same name in the British Pharmacopœia.

It is composed of the Exsiccated Sodium Phosphate, Sodium Bicarbonate, and Tartaric and Citric acids. It contains just sufficient sodium bicarbonate to neutralize the tartaric and citric acids when it is dissolved in water, and the carbonic acid gas liberated gives a pleasant acidulous and effervescent taste.

**Dose.**—“Average dose: 8 Gm. (120 grains).” (U. S. P.)

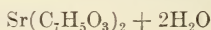
It should be kept in well stoppered bottles.

**SODII PHOSPHAS EXSICCATUS.****Exsiccated Sodium Phosphate.**

This is also called anhydrous sodium phosphate; it is obtained by driving off the water of crystallization of Sodium Phosphate (U. S. P.), which amounts to 60.3 per cent of the latter's weight. In a given weight of the exsiccated salt there are two and a half times as much sodium phosphate as in the same weight of the crystallized salt.

It is a white powder which absorbs moisture readily when exposed to the air and is gradually transformed into a salt of the composition  $\text{Na}_2\text{HPO}_4 + 7\text{H}_2\text{O}$ , which contains about 47 per cent of water; the latter salt is permanent.

**Dose.**—“Average dose: 1 Gm. (15 grains).” (U. S. P.)

**STRONTII SALICYLAS.****Strontium Salicylate.**

**Character.**—White, crystalline powder, odorless and having a sweetish saline taste.

**Solubility.**—Soluble in water (1:18) and alcohol (1:66), much more so when these are boiling.

**Incompatibility.**—Incompatible with ferric salts, mineral acids, quinine salts in solution, spirit of nitrous ether, and sodium phosphate in powder.

**Dose.**—“Average dose: 1 Gm. (15 grains).” (U. S. P.)

Keep in well stoppered bottles, protected from heat and light.

Strontium Lactate (U. S. P., 1890) has been dismissed from the Pharmacopœia; the bromide and iodide are retained.



**STROPHANTHINUM.****Strophanthin.**

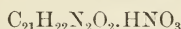
A glucoside or mixture of glucosides, obtained from *Strophanthus*.

**Character.**—A white or faintly yellowish crystalline powder, containing varying amounts of water of crystallization. Permanent in the air. Taste intensely bitter; great caution should be used in tasting it.

**Solubility.**—Very soluble in water and diluted alcohol.

**Dose.**—“Average dose: 0.0003 Gm. = 0.3 milligramme ( $\frac{1}{300}$  grain).” (U. S. P.)

**Caution.**—Keep in well stoppered amber colored bottles. Its solutions are very liable to decompose and should be freshly prepared. Exceedingly powerful poison. There is no known chemical assay for this drug and, as it is liable to variation, physicians would do well to secure specimens which have been tested physiologically.

**STRYCHNINE NITRAS.****Strychnine Nitrate.**

**Character.**—Colorless, glistening needles, odorless, and having an intensely bitter taste; permanent in the air.

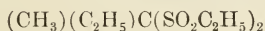
**Solubility.**—Soluble in water (1:42), alcohol (1:120), and glycerin (1:60); much more soluble in warm water or alcohol.

The hydrochloride (the only strychnine salt official in the Br. P.) and the Sulphate (already official in the U. S. P.) both contain water of crystallization and effloresce in dry air. The Nitrate (the only salt official in the P. G.) contains no water of crystallization and is permanent in the air.

**Dose.**—“Average dose: 0.001 Gm. = 1 milligramme ( $\frac{1}{54}$  grain).” (U. S. P.)

**SULPHONETHYLMETHANUM.****Sulphonethylmethane.**

(*Trional.*)



This substance is commonly known by the trade name, *trional*. It is official in the German Pharmacopœia under the name Methylsulfonyl-methane; in the French and Swedish Pharmacopœias it is called *Trional*, and in the Austrian Pharmacopœia, *Trionalum*. It should not be confused with Sulphonmethanum (q. v.) (*sulphonal*).

**Chemistry.**—Chemically it is diethylsulphonemethylethylmethane ( $(\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}) > C < \begin{matrix} SO_2C_2H_5 \\ SO_2C_2H_5 \end{matrix}$ ) and may be regarded as methane ( $CH_4$ ) in which two hydrogen atoms are replaced by ethylsulphone ( $SO_2C_2H_5$ )

groups, one by a methyl ( $\text{CH}_3$ ) and the fourth by an ethyl ( $\text{C}_2\text{H}_5$ ) group. (For method of preparation see Sulphonmethanum.)

**Character.**—"Colorless, lustrous, odorless, crystalline scales which have a bitter taste in aqueous solution."

**Solubility.**—"Soluble in 195 parts of water, more readily in boiling water, and readily soluble in alcohol and ether."

It melts at  $76^\circ \text{C}$ .; hence if a test-tube containing some of the powder be placed in hot water, the substance will melt; Sulphonmethanum (the melting point of which is  $125.5^\circ \text{C}$ .) will not melt under these circumstances.

The aqueous solution should be neutral to litmus paper; no odor should be evolved when 1 Gm. is dissolved in 50 Cc. of boiling water.

**Dose.**—"Average dose: 1 Gm. (15 grains)." (U. S. P.)

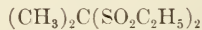
The German Pharmacopœia fixes 2 Gm. as the largest single dose and 4 Gm. as the maximum amount to be given in one day.

**Caution.**—Should not be combined in full dose with full doses of other drugs of similar physiological action, e. g., Hydrated Chloral, Chloralformamide, Sulphonmethane, etc.

### SULPHONMETHANUM.

#### Sulphonmethane.

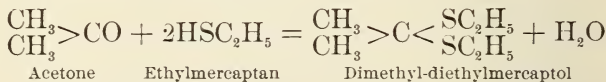
(*Sulphonal*.)



This substance is commonly known by the trade name, *sulphonal*—a name which has been adopted by the British and several other Pharmacopœias. It should not be confused with Sulphonethylmethanum (q. v.).

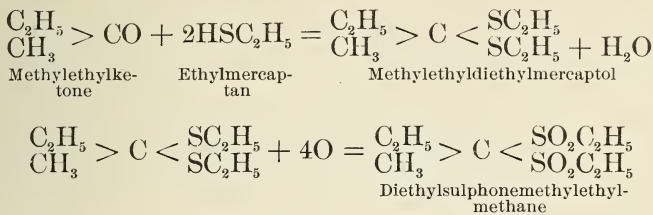
**Chemistry.**—Chemically it is diethylsulphonedimethylmethane

$\begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix} > \text{C} < \begin{matrix} \text{SO}_2\text{C}_2\text{H}_5 \\ \text{SO}_2\text{C}_2\text{H}_5 \end{matrix}$  The chemical structure of this substance, as well as that of Sulphonethylmethane, is explained by the following reactions involved in one process of its manufacture: acetone and ethylmercaptan unite (under the influence of dry hydrochloric acid gas) to form dimethyldiethylmercaptol



Through oxidation with potassium permanganate the sulphur atoms combine with oxygen to form sulphone ( $\text{SO}_2$ ) groups; the resulting product is diethylsulphonedimethylmethane  $(\text{CH}_3)_2\text{C}(\text{SO}_2\text{C}_2\text{H}_5)_2$ —a name shortened in the Pharmacopœia to Sulphonmethane. It may be regarded as methane ( $\text{CH}_4$ ) in which two hydrogen atoms are replaced by methyl ( $\text{CH}_3$ ) groups and two by ethylsulphone ( $\text{SO}_2\text{C}_2\text{H}_5$ ) groups.

If methylethylketone  $\frac{C_2H_5}{CH_3} > CO$  be used in the above process instead of acetone, diethylsulphonemethylethylmethane (Sulphonethylmethanum, U. S. P.) is formed:



The chemical name is abbreviated by the Pharmacopœia to "Sulphonethylmethane" which is commonly known as *trional*; the *tri* of the latter name indicates the presence of three ethyl ( $C_2H_5$ ) groups. If two ethyl groups are introduced in the place of the methyl groups, the resulting compound  $\frac{C_2H_5}{C_2H_5} > C < \frac{SO_2C_2H_5}{SO_2C_2H_5}$  is what is commonly known as *tetronal*; the latter name indicates the presence of four ethyl groups. As a general rule, the introduction of ethyl groups into a compound increases the hypnotic action.

**Character.**—Colorless, odorless, and nearly tasteless prismatic crystals, permanent in the air.

**Solubility.**—Soluble in water (1:360) and in alcohol (1:47), much more so in boiling water (1:15) and boiling alcohol (1:2). It melts at  $125.5^\circ C$ . A pure preparation is neutral to litmus and evolves no odor when boiled with water.

**Dose.**—"Average dose: 1 Gm. (15 grains)." (U. S. P.)

The German Pharmacopœia fixes the maximum single dose at 2 Gm.; the maximum daily dose at 4 Gm. Kast recommends that not more than 2 Gm. be given to a man nor more than 1 Gm. to a woman at a single dose, and that if the drug is used for any length of time the administration be frequently discontinued for from one to several days. The urine should be watched, and if there are indications of hæmaturia the use of the drug should be discontinued.

## SYRUPUS HYPOPHOSPHITUM COMPOSITUS.

### Compound Syrup of Hypophosphites.

Syrupus Hypophosphitum cum Ferro (U. S. P., 1890), is dropped, but this may take its place, as it contains iron (although in considerably smaller proportion). It contains 5 hypophosphites, Hypophosphorous Acid, Quinine, and Strychnine. It is adopted (with slight changes) from the National Formulary and is similar to a number of well-known commercial articles.

**Dose.**—"Average dose: 8 Cc. (2 fluidrachms)." (U. S. P.)

**TALCUM.****Talc.**

A native hydrous magnesium silicate, official under the same name in the German Pharmacopœia. The German Pharmacopœia contains a dusting powder Pulvis salicylicus cum Talco consisting of salicylic acid, starch, and talc; some of the commercial talcum powders contain talc and boracic acid.

**Properties.**—Talc occurs as a grayish-green solid with waxy luster, or a white or pale gray powder. It feels greasy to the touch, hence it is popularly called soapstone. It is used as a dusting powder, and in some pill masses.

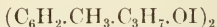
**TALCUM PURIFICATUM.****Purified Talc.**

Talcum purified by treatment with hydrochloric acid. Used in the pharmacopœial method of preparing certain official waters of volatile oils.

The same preparation is to be found in the National Formulary.

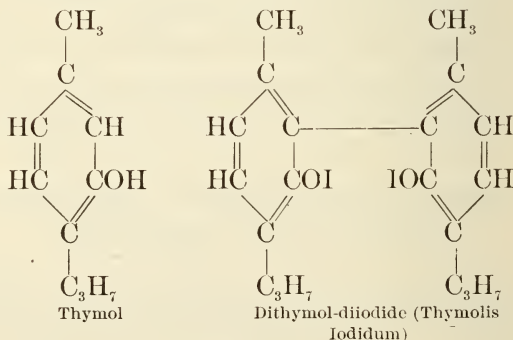
**THYMOLIS IODIDUM.****Thymol Iodide.**

(*Aristol.*)



Official in the French Pharmacopœia as Diiodothymol. Various known as *aristol*, *annidalin*, and *thymotol*.

**Chemistry.**—Chemically it is dithymol-diiodide. It is obtained by the condensation of two molecules of thymol (a methylisopropylphenol) and the introduction into its phenolic group of two atoms of iodine:



**Character.**—A bright, chocolate-colored or reddish-yellow, bulky powder, almost tasteless, and having a slight aromatic odor.

**Solubility.**—Insoluble in water and glycerin, soluble with difficulty in alcohol, readily soluble in fatty oils and in ether, vaseline, chloroform, and collodion.



It contains 46.14 per cent of iodine (Iodoform contains 96.7 per cent, Iodol 89 per cent of iodine).

**Caution.**—Keep in amber-colored bottles, protected from light.

**Other thymol derivatives.**—Many other derivatives or compounds of thymol have been suggested for therapeutic use, e. g., *thymotal* (thymol-carbonate), *thymacetin* (analogous to *phenacetin*), *thymoform* (condensation product of thymol and formaldehyde), *iodothymoform* (iodized *thymoform*), mercury compounds of thymol, *thymosalol*, etc.

#### TINCTURA GAMBIR COMPOSITA.

Compound Tincture of Gambir.

To replace Tinctura Catechu Composita (U. S. P., 1890). (See Gambir.)

**Dose.**—“Average dose: 4 Cc. (1 fluidrachm).” (U. S. P.)

#### TINCTURA LIMONIS CORTICIS.

Tincture of Lemon Peel.

Similar to the Tinctura Limonis (Br. P.), but twice as strong.

#### TROCHISCI GAMBIR.

Troches of Gambir.

To replace Trochisci Catechu (U. S. P., 1890).

#### UNGUENTUM ACIDI BORICI.

Ointment of Boric Acid.

A 10 per cent ointment made with Paraffin and White Petrolatum. Similar to the Unguentum Acidi Borici of the British and German Pharmacopœias.

#### UNGUENTUM HYDRARGYRI DILUTUM.

Blue Ointment.

This preparation contains 67 per cent of Unguentum Hydrargyri, which is called Mercurial Ointment. Heretofore “Blue Ointment” and “Mercurial Ointment” have been synonymous. Mercurial Ointment contains about 50 per cent of metallic mercury, while Blue Ointment contains about 33.5 per cent.

#### UNGUENTUM ZINCI STEARATIS.

Ointment of Zinc Stearate.

An ointment containing 50 per cent of Zinc Stearate. The zinc present in the ointment is equivalent to about 7.5 or 8 per cent of zinc oxide.

## VANILLINUM.

## Vanillin.



Methyl ether of protocatechuic aldehyde  $C_6H_3 \begin{matrix} \diagup CHO \text{ (1)} \\ - OCH_3 \text{ (3)} \\ \diagdown OH \text{ (4)} \end{matrix}$ , occurring naturally in vanilla or made synthetically. Vanilla (U. S. P.) contains from 1 to 2 or 3 per cent of vanillin.

Eugenol, the principal constituent of oil of cloves, is allylmethyl pyrocatechol, and by oxidation yields vanillin, the allyl group being oxidized to the aldehyde group, (CHO), present in vanillin.

**Character.**—Colorless, prismatic needles, having the odor and taste of vanilla, and melting at  $80^\circ$  to  $81^\circ$  C.

**Solubility.**—Soluble in cold water (about 1:100), in warm (1:15), easily soluble in alcohol, glycerin, ether, and chloroform.

Being a phenol in character, it readily dissolves in dilute alkali hydroxides, from which it is precipitated by acids. It is extracted completely from its solution in ether by shaking with a saturated aqueous solution of sodium bisulphite, from which it may be precipitated again by sulphuric acid.

**Purity.**—The Pharmacopœia guards against a possible adulteration with acetanilide by the following test: on warming 0.1 Gm. of Vanillin with concentrated alcoholic solution of sodium hydroxide, adding chloroform and again warming it should not give the disgusting odor of phenyl isocyanide; such an odor would indicate acetanilide.

**Dose.**—“Average dose: 0.030 Gm.=30 milligrammes ( $\frac{1}{2}$  grain).” (U. S. P.)

**Caution.**—Keep in well-stoppered bottles, in a cool place, and protected from the light.

Coumarin  $\left( C_6H_4 \begin{matrix} \diagup O-CO \\ | \\ \diagdown CH=CH \end{matrix} \right)$  the anhydride of orthocinnamic acid

is an odoriferous principle found in the Tonka bean (1.5 per cent), and elsewhere, which resembles vanillin in odor. It forms colorless, shining prisms, melting at  $67^\circ$  C., and soluble in 400 parts cold, 45 parts of hot water, and in 7.5 parts of alcohol, easily soluble in ether.

“Extracts of vanilla” are sometimes found to be made not from the true vanilla bean, but to be alcoholic tinctures of synthetic vanillin or coumarin. Such sophistication can readily be detected, as follows: If some of the extract be freed from alcohol by evaporation, made up to its original volume with water and acidified with acetic acid, a reddish brown precipitate of resin will form in the case of a true extract; absence of such resin would indicate an artificial extract. The filtrate from this resin, in a true extract, should give a copious precipitate with basic lead acetate solution; an artificial gives none.

Distinction between vanillin and coumarin: an aqueous solution of vanillin is turned blue by a few drops of ferric chloride solution (U. S. P. test), coumarin is not. An aqueous solution of coumarin, unlike vanillin, forms a precipitate, when iodine in potassium iodide is added in excess, at first brown and flocculent, and afterwards, on shaking, forming a dark-green curdy clot.

A case has recently been reported in which vanillin was adulterated (to the extent of 50 per cent) with terpin hydrate; the adulteration was readily detected by the lack of a definite melting point.

### VINUM COCÆ.

#### Wine of Coca.

An official wine prepared from the Fluidextract of Coca; it may well replace some of the commercial articles of this name.

**Dose.**—“Average dose: 16 Cc. (‡ fluidrachms).” (U. S. P.)

This is practically the same preparation as the Vinum Erythroxyli, N. F.

### ZINCI PHENOLSULPHONAS.

#### Zinc Phenolsulphonate.



Commonly known as zinc sulphocarbolate; official in British Pharmacopœia as Zinci Sulphocarbolas. It should contain not less than 99.5 per cent of pure zinc paraphenolsulphonate.  $(\text{C}_6\text{H}_4(\text{OH})\text{SO}_3)_2\text{Zn} 1:4 + 8\text{H}_2\text{O}$ .

**Character.**—Colorless, transparent, rhombic prisms, or tabular crystals, odorless, and having an astringent, metallic taste; effloresces on exposure and may become pink.

**Solubility.**—Easily soluble in water or alcohol. The aqueous solution is acid to litmus.

**Dose.**—“Average dose: 0.125 Gm. = 125 milligrammes (2 grains).” (U. S. P.)

**Caution.**—Keep in small, well-stoppered bottles.

### ZINCI STEARAS.

#### Zinc Stearate.

Used in preparing Unguentum Zinci Stearatis.

# CHANGES IN STRENGTH OF THE MORE IMPORTANT OFFICIAL PREPARATIONS.

(a) *Table of More Important Pharmacopœial Preparations, the Strength of which has been Increased.*

TITLE.	CHIEF CONSTITUENT.	PHARMACOPŒIA, 1890.	EIGHTH DECENNIAL REVISION.
Acidum Sulphuricum Aromaticum .....	H <sub>2</sub> SO <sub>4</sub> , by weight.....	About 18.5 per cent.....	About 20.0 per cent.
Alcohol .....	Absolute Alcohol, by weight.....	About 91.0 per cent.....	About 92.3 per cent.
Alcohol Dilutum.....	Absolute Alcohol, by weight.....	About 41.0 per cent.....	About 41.5 per cent.
Caffeina Citrata Effervescescens.....	Citrated Caffeine, by weight.....	2.0 Gm. in 100 Gm.....	4.0 Gm. in 100 Gm.
Extractum Opii .....	Morphine (cryst.), by weight.....	18.0 per cent.....	20.0 per cent.
Liquor Ferri et Ammonii Acetatis.....	Tincture of Ferric Chloride.....	2 Ce. in 100 Ce.....	1 Ce. in 100 Ce.
Liquor Ferri Tersulphatis.....	Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> , by weight.....	28.7 per cent.....	36.0 per cent.
Manganii Dioxidum Præcipitatum <i>a</i> .....	Manganese Dioxide.....	At least 66.0 per cent.....	At least 80.0 per cent.
Oleatum Hydrargyri .....	Yellow Mercuric Oxide, by weight.....	20.0 per cent.....	25.0 per cent.
Tinctura Aurantii Dulcis.....	Sweet Orange Peel.....	1 Gm. in 5.0 Ce.....	1 Gm. in 2.0 Ce.
Tinctura Calumbæ.....	Calumba.....	1 Gm. in 10.0 Ce.....	1 Gm. in 5.0 Ce.
Tinctura Cantharidis.....	Cantharides.....	1 Gm. in 20.0 Ce.....	1 Gm. in 10.0 Ce.
Tinctura Capsici.....	Capsicum.....	1 Gm. in 20.0 Ce.....	1 Gm. in 10.0 Ce.
Tinctura Cardamomi.....	Cardamom.....	1 Gm. in 10.0 Ce.....	1 Gm. in 5.0 Ce.
Tinctura Cinnamomi.....	Saigon Cinnamon.....	1 Gm. in 10.0 Ce.....	1 Gm. in 5.0 Ce.
Tinctura Quassie.....	Quassia.....	1 Gm. in 10.0 Ce.....	1 Gm. in 5.0 Ce.
Tinctura Rhei.....	Rhubarb.....	1 Gm. in 10.0 Ce.....	1 Gm. in 5.0 Ce.
Tinctura Serpentarie.....	Serpentaria.....	1 Gm. in 10.0 Ce.....	1 Gm. in 5.0 Ce.
Tinctura Strophanthi .....	Strophanthus.....	1 Gm. in 10.0 Ce.....	1 Gm. in 10.0 Ce.
Tinctura Tolutana .....	Balsam of Tolu.....	1 Gm. in 20.0 Ce.....	1 Gm. in 10.0 Ce.
Unguentum Chrysarobini.....	Chrysarobin, by weight.....	About 5.0 per cent.....	1 Gm. in 5.0 Ce.
Vinum Ergotæ .....	Fluidextract Ergot.....	1 Gm. in 6.57 Ce.....	About 6.0 per cent. 1 Ce. Fluidextract Ergot in 5 Ce.

<sup>a</sup> See page 46.



(b) Table of More Important Pharmacopœical Preparations, the Strength of which has been Decreased.

TITLE.	CHIEF CONSTITUENT.	PHARMACOPŒIA, 1890.	EIGHTH DECENNIAL REVISION.
Calx Chlorinata	Available Cl, by weight.	At least 35.0 per cent.	At least 30.0 per cent.
Jalap	Alcohol-soluble resin, by weight.	12.0 per cent.	At least 8.0 per cent.
Liquor Ferri Chloridi	Ether-soluble resin, by weight.	Not more than 1.2 per cent.	Not more than 1.5 per cent.
Lithii Citras Effervescens	Anhydrous FeCl <sub>3</sub> , by weight.	37.8 per cent.	29.0 per cent.
Opii Pulvis	Lithium Citrate, by weight.	About 17.0 per cent.	About 5.0 per cent.
Opium Deodoratum	Morphine (cryst.), by weight.	13 to 15 per cent.	12 to 12.5 per cent.
Potassii Citras Effervescens	Morphine (cryst.), by weight.	About 48.0 per cent.	12 to 12.5 per cent.
Spiritus Frumenti	Potassium Citrate, by weight.	44 to 50 per cent.	About 20.0 per cent.
Suppositoria Glycerini	Absolute Alcohol, by weight.	6 Gm. each	37 to 47.5 per cent.
Syrupus Ferri Iodidi	Glycerin, (half their former size)	About 10 per cent.	3 Gm. each.
Tinctura Aconiti	Ferrous Iodide, by weight.	About 10 per cent.	About 5 per cent.
Tinctura Belladonnæ Foliorum	Aconite.	1 Gm. in 2.85 Cc.	1 Gm. in 10.0 Cc.
Tinctura Benzoini Composita	Belladonna Leaves.	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.
Tinctura Cannabidis Indicæ	Benzoin	1 Gm. in 8.33 Cc.	1 Gm. in 10.0 Cc.
Tinctura Colchicis Seminis	Indian Cannabis	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.
Tinctura Digitalis	Colchicum Seed	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.
Tinctura Ferri Chloridi	Digitalis.	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.
Tinctura Gambir Composita <sup>a</sup>	Anhydrous FeCl <sub>3</sub> , by weight	13.6 per cent.	13.28 per cent.
Tinctura Gelsemii	Gambir	1 Gm. in 10.0 Cc.	1 Gm. in 20.0 Cc.
Tinctura Hyoscyami	Gelsemium	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.
Tinctura Kino	Hyoscyamus.	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.
Tinctura Lobeliæ	Kino	1 Gm. in 10.0 Cc.	1 Gm. in 20.0 Cc.
Tinctura Opii	Lobelia.	1 Gm. in 5.0 Cc.	1 Gm. in 10.0 Cc.
Tinctura Opii Deodorata	Morphine (cryst.), by weight	1.3 to 1.5 Gm. in 100 Cc.	1.2 to 1.25 Gm. in 100 Cc.
Tinctura Physostigmatis	Morphine (cryst.), by weight	1.3 to 1.5 Gm. in 100 Cc.	1.2 to 1.25 Gm. in 100 Cc.
Tinctura Sanguinaria	Physostigma	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.
Tinctura Scillæ	Sanguinaria	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.
Tinctura Stramonii	Squill	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.
	Stramonium.	1 Gm. in 6.67 Cc.	1 Gm. in 10.0 Cc.

<sup>a</sup> See Gambir, p. 37.

(b) Table of More Important Pharmacopoeial Preparations, the Strength of which has been Decreased—Continued.

TITLE.	CHIEF CONSTITUENT.	PHARMACOPŒIA, 1890.	EIGHTH DECENNIAL REVISION.
Tinctura Veratril . . . . .	Veratrum . . . . .	1 Gm. in 2.5 Cc . . . . .	1 Gm. in 10.0 Cc.
Trochiscus Gubebæ . . . . .	Oleoresin of Cubebs, by weight . . . . .	0.04 Gm. in each . . . . .	0.02 Gm. in each.
Unguentum Phenolis . . . . .	Phenol, by weight . . . . .	About 5.0 per cent. . . . .	About 3.0 per cent.
Unguentum Sulphuris. . . . .	Washed Sulphur, by weight . . . . .	About 30.0 per cent. . . . .	About 15.0 per cent.
Vinum Albann . . . . .	Absolute Alcohol, by weight. . . . .	10.0 to 14.0 per cent. . . . .	7.0 to 12.0 per cent.
Vinum Colecheli Seminis . . . . .	Fluidextract Colechicum Seed. . . . .	1 Gm. Colechicum Seed in 6.67 Cc . . . . .	1 Cc. Fluidextract Colechicum Seed in 10.0 Cc.
Vinum Eubranii . . . . .	Absolute Alcohol, by weight. . . . .	10.0 to 14.0 per cent. . . . .	7.0 to 12.0 per cent.

(c) Table of More Important Pharmacopœial Preparations, for which a Standard has been Fixed, or made More Definite.

TITLE.	CHIEF CONSTITUENT.	PHARMACOPEIA, 1890.	EIGHTH DECENNIAL REVISION.
Aconitum.....	Aconitine, by weight.....	Standard not fixed.....	At least 0.5 per cent.
Belladonnæ Folia.....	Mydriatic alkaloids, by weight.....	Standard not fixed.....	At least 0.35 per cent.
Belladonnæ Radix.....	Mydriatic alkaloids, by weight.....	Standard not fixed.....	At least 0.5 per cent.
Cinchona.....	Alkaloids, by weight.....	At least 2.5 per cent Quinine.....	At least 4 per cent ether-soluble alkaloids.
Coca.....	Ether-soluble alkaloids, by weight.....	Standard not fixed.....	At least 0.5 per cent.
Colechici Cormus.....	Colechicine, by weight.....	Standard not fixed.....	At least 0.35 per cent.
Colechici Semen.....	Colechicine, by weight.....	Standard not fixed.....	At least 0.55 per cent.
Conium.....	Coniine, by weight.....	Standard not fixed.....	At least 0.5 per cent.
Emplastrum Belladonnæ.....	Mydriatic alkaloids, by weight.....	Standard not fixed.....	Not less than 0.38 per cent nor more than 0.42 per cent.
Extractum Belladonnæ.....	Mydriatic alkaloids, by weight.....	Standard not fixed.....	1.4 per cent.
Extractum Colechici Cormi.....	Colechicine, by weight.....	Standard not fixed.....	1.4 per cent.
Extractum Hyoscyami.....	Mydriatic alkaloids, by weight.....	Standard not fixed.....	0.3 per cent.
Extractum Nuclei Vomice.....	Strychnine, by weight.....	15.0 per cent total alkaloids.....	5.0 per cent.
Extractum Physostigmatis.....	Ether-soluble alkaloids, by weight.....	Standard not fixed.....	2.0 per cent.
Extractum Stramonii.....	Mydriatic alkaloids, by weight.....	Standard not fixed.....	1.4 per cent.
Fluidextractum Aconiti.....	Aconitine, by weight.....	Standard not fixed.....	0.4 Gm. in 100 Cc.
Fluidextractum Belladonnæ Radicis.....	Mydriatic alkaloids, by weight.....	Standard not fixed.....	0.5 Gm. in 100 Cc.
Fluidextractum Cinchonæ.....	Anhydrous ether-soluble alkaloids, by weight.....	Standard not fixed.....	4.0 Gm. in 100 Cc.
Fluidextractum Cocce.....	Ether-soluble alkaloids, by weight.....	Standard not fixed.....	0.5 Gm. in 100 Cc.
Fluidextractum Colechici Seminis.....	Colechicine, by weight.....	Standard not fixed.....	0.5 Gm. in 100 Cc.
Fluidextractum Comii.....	Coniine, by weight.....	Standard not fixed.....	0.45 Gm. in 100 Cc.
Fluidextractum Guaraniæ.....	Alkaloids, by weight.....	Standard not fixed.....	3.5 Gm. in 100 Cc.
Fluidextractum Hydrastis.....	Hydrastine, by weight.....	Standard not fixed.....	2.0 Gm. in 100 Cc.
Fluidextractum Hyoscyami.....	Mydriatic alkaloids, by weight.....	Standard not fixed.....	0.075 Gm. in 100 Cc.
Fluidextractum Ipecacuanhæ.....	Alkaloids, by weight.....	Standard not fixed.....	1.75 Gm. in 100 Cc.
Fluidextractum Nuclei Vomiceæ.....	Strychnine, by weight.....	1.5 Gm. total alkaloids in 100 Cc.....	1.0 Gm. in 100 Cc.
Fluidextractum Pilocarpi.....	Alkaloids, by weight.....	Standard not fixed.....	0.4 Gm. in 100 Cc.
Fluidextractum Stramonii.....	Mydriatic alkaloids, by weight.....	Standard not fixed.....	0.35 Gm. in 100 Cc.

(c) *Table of More Important Pharmacopœial Preparations, for which a Standard has been Fixed, etc.—Continued.*

TITLE.	CHIEF CONSTITUENT.	PHARMACOPŒIA, 1890.	EIGHTH DECENIAL REVISION.
Guarana.....	Alkaloids, by weight.....	Standard not fixed.....	At least 3.5 per cent.
Hydrastis.....	Hydrastine, by weight.....	Standard not fixed.....	At least 2.5 per cent.
Hyoscyamus.....	Mydratic alkaloids, by weight.....	Standard not fixed.....	At least 0.08 per cent.
Ipecacuanha.....	Alkaloids, by weight.....	Standard not fixed.....	At least 2.0 per cent.
Jalap.....	{Alcohol-soluble resin, by weight.....	12 per cent.....	At least 8.0 per cent.
Nux Vomica.....	{Ether-soluble resin, by weight.....	Not more than 1.2 per cent.....	Not more than 1.5 per cent.
	{Strychnine, by weight.....	Standard not fixed.....	At least 1.25 per cent.
Oleum Amygdalæ Amaræ.....	{Benzaldehyde, by weight.....	Standard not fixed.....	At least 85.0 per cent.
	{Hydrocyanic Acid, by weight.....	Standard not fixed.....	2 to 4 per cent.
Oleum Cajuputi.....	Cineol, by volume.....	Standard not fixed.....	At least 55 per cent.
Oleum Caryophylli.....	Eugenol, by volume.....	Standard not fixed.....	At least 80 per cent.
Oleum Cinnamoni.....	Cinnamic Aldehyde, by volume.....	Standard not fixed.....	At least 75 per cent.
Oleum Eucalypti.....	Cineol, by volume.....	Standard not fixed.....	At least 50 per cent.
Oleum Limonis.....	Citral, by weight.....	Standard not fixed.....	At least 4 per cent.
Oleum Menthæ Piperitæ.....	{Menthyl Acetate, by weight.....	Standard not fixed.....	At least 8 per cent.
	{Total Menthol, by weight.....	Standard not fixed.....	At least 50 per cent.
Oleum Pimentæ.....	Eugenol, by volume.....	Standard not fixed.....	At least 65 per cent.
Oleum Rosmarini.....	{Bornyl Acetate, by weight.....	Standard not fixed.....	At least 5 per cent.
	{Total Borneol, by weight.....	Standard not fixed.....	At least 15 per cent.
Oleum Santali.....	Santalol, by weight.....	Standard not fixed.....	At least 90 per cent.
Oleum Thymi.....	Phenols, by volume.....	Standard not fixed.....	At least 20 per cent.
Pancreatinum.....	.....	Standard not fixed.....	1 part digests at least 25 parts of starch.
Physostigma.....	Ether-soluble alkaloids, by weight.....	Standard not fixed.....	At least 0.15 per cent.
Pilocarpus.....	Alkaloids, by weight.....	Standard not fixed.....	At least 0.5 per cent.
Stramonium.....	Mydratic alkaloids, by weight.....	Standard not fixed.....	At least 0.35 per cent.
Tinctura Aconiti.....	Aconitine, by weight.....	Standard not fixed.....	0.045 Gm. in 100 Cc.
Tinctura Belladonnæ Foliorum.....	Mydratic alkaloids, by weight.....	Standard not fixed.....	0.035 Gm. in 100 Cc.
Tinctura Colechicæ Sembaliis.....	Colechicine, by weight.....	Standard not fixed.....	0.05 Gm. in 100 Cc.
Tinctura Hydrastis.....	Hydrastine, by weight.....	Standard not fixed.....	0.4 Gm. in 100 Cc.
Tinctura Hyoscyami.....	Mydratic alkaloids, by weight.....	Standard not fixed.....	0.007 Gm. in 100 Cc.
Tinctura Nucis Vomica.....	Strychnine, by weight.....	0.3 Gm. total alkaloids in 100 Cc.....	0.1 Gm. Strychnine in 100 Cc.
Tinctura Physostigmatis.....	Ether-soluble alkaloids, by weight.....	Standard not fixed.....	0.014 Gm. in 100 Cc.



## CHANGES IN OFFICIAL LATIN TITLES OF PHARMACOPŒIAL PREPARATIONS.

Pharmacopœia, 1890.	Pharmacopœia, Eighth Revision.
Acidum Arsenosum .....	Arseni Trioxidum.
Acidum Carbolicum.....	Phenol.
Acidum Chromicum .....	Chromii Trioxidum.
Aloe Barbadosensis.....	Aloe.
Aloe Socotrina.....	Aloe.
Alumini Hydras.....	Alumini Hydroxidum.
Ammonii Valerianas .....	Ammonij Valeras.
Amyl Nitris .....	Amylis Nitris.
Apomorphinæ Hydrochloras .....	Apomorphinæ Hydrochloridum.
Aqua Chlori .....	Liquor Chlori Compositus.
Argentii Nitras Dilutus .....	Argentii Nitras Mitigatus.
Arnicae Flores .....	Arnica.
Calx Chlorata .....	Calx Chlorinata.
Chloral.....	Chloralum Hydratum.
Cocainæ Hydrochloras .....	Cocainæ Hydrochloridum.
Colchici Radix .....	Colchici Cormus.
Emplastrum Resinæ.....	Emplastrum Adhæsivum.
Extractum Aconiti Fluidum .....	Fluidextractum Aconiti.
Extractum Apocyni Fluidum .....	Fluidextractum Apocyni.
Extractum Aromaticum Fluidum.....	Fluidextractum Aromaticum.
Extractum Aurantii Amari.....	Fluidextractum Aurantii Amari.
Extractum Belladonnæ Foliorum Alcoholicum....	Extractum Belladonnæ Foliorum.
Extractum Belladonnæ Radicis Fluidum.....	Fluidextractum Belladonnæ Radicis.
Extractum Buchu Fluidum .....	Fluidextractum Buchu.
Extractum Calami Fluidum.....	Fluidextractum Calami.
Extractum Calumbæ Fluidum .....	Fluidextractum Calumbæ.
Extractum Cannabis Indicæ Fluidum .....	Fluidextractum Cannabis Indicæ.
Extractum Capsici Fluidum.....	Fluidextractum Capsici.
Extractum Chimaphilæ Fluidum .....	Fluidextractum Chimaphilæ.
Extractum Chiratæ Fluidum .....	Fluidextractum Chiratæ.
Extractum Cimicifugæ Fluidum .....	Fluidextractum Cimicifugæ.
Extractum Cinchonæ Fluidum.....	Fluidextractum Cinchonæ.
Extractum Cocæ Fluidum .....	Fluidextractum Cocæ.
Extractum Colchici Radicis.....	Extractum Colchici Cormi.
Extractum Colchici Seminis Fluidum.....	Fluidextractum Colchici Seminis.
Extractum Conii Fluidum .....	Fluidextractum Conii.
Extractum Convallariæ Fluidum .....	Fluidextractum Convallariæ.
Extractum Cubebæ Fluidum.....	Fluidextractum Cubebæ.
Extractum Cypripedii Fluidum.....	Fluidextractum Cypripedii.
Extractum Digitalis Fluidum.....	Fluidextractum Digitalis.
Extractum Ergotæ Fluidum .....	Fluidextractum Ergotæ.
Extractum Eriodictyi Fluidum .....	Fluidextractum Eriodictyi.
Extractum Eucalypti Fluidum.....	Fluidextractum Eucalypti.
Extractum Eupatorii Fluidum.....	Fluidextractum Eupatorii.
Extractum Frangulæ Fluidum.....	Fluidextractum Frangulæ.
Extractum Gelsemii Fluidum.....	Fluidextractum Gelsemii.

## Changes in official Latin titles of pharmacopœial preparations—Continued.

Pharmacopœia, 1890.	Pharmacopœia, Eighth Revision.
Extractum Gentianæ Fluidum.....	Fluidextractum Gentianæ.
Extractum Geranii Fluidum.....	Fluidextractum Geranii.
Extractum Glycyrrhizæ Fluidum.....	Fluidextractum Glycyrrhizæ.
Extractum Grindeliæ Fluidum.....	Fluidextractum Grindeliæ.
Extractum Guaranæ Fluidum.....	Fluidextractum Guaranæ.
Extractum Hamamelidis Fluidum.....	Fluidextractum Hamamelidis Foliorum.
Extractum Hydrastis Fluidum.....	Fluidextractum Hydrastis.
Extractum Hyoscyami Fluidum.....	Fluidextractum Hyoscyami.
Extractum Ipecacuanhæ Fluidum.....	Fluidextractum Ipecacuanhæ.
Extractum Krameriæ Fluidum.....	Fluidextractum Krameriæ.
Extractum Lappæ Fluidum.....	Fluidextractum Lappæ.
Extractum Leptandræ Fluidum.....	Fluidextractum Leptandræ.
Extractum Lobeliæ Fluidum.....	Fluidextractum Lobeliæ.
Extractum Lupulini Fluidum.....	Fluidextractum Lupulini.
Extractum Matico Fluidum.....	Fluidextractum Matico.
Extractum Mezerei Fluidum.....	Fluidextractum Mezerei.
Extractum Nucis Vomiciæ Fluidum.....	Fluidextractum Nucis Vomiciæ.
Extractum Pareiræ Fluidum.....	Fluidextractum Pareiræ.
Extractum Phytolacæ Radicis Fluidum.....	Fluidextractum Phytolacæ.
Extractum Pilocarpi Fluidum.....	Fluidextractum Pilocarpi.
Extractum Podophylli Fluidum.....	Fluidextractum Podophylli.
Extractum Pruni Virginianæ Fluidum.....	Fluidextractum Pruni Virginianæ.
Extractum Quassiæ Fluidum.....	Fluidextractum Quassiæ.
Extractum Rhamni Purshianæ Fluidum.....	Fluidextractum Rhamni Purshianæ.
Extractum Rhei Fluidum.....	Fluidextractum Rhei.
Extractum Rhois Glabræ Fluidum.....	Fluidextractum Rhois Glabræ.
Extractum Rosæ Fluidum.....	Fluidextractum Rosæ.
Extractum Rubi Fluidum.....	Fluidextractum Rubi.
Extractum Sabinæ Fluidum.....	Fluidextractum Sabinæ.
Extractum Sanguinaræ Fluidum.....	Fluidextractum Sanguinaræ.
Extractum Sarsaparillæ Fluidum.....	Fluidextractum Sarsaparillæ.
Extractum Sarsaparillæ Fluidum Compositum.....	Fluidextractum Sarsaparillæ Compositum.
Extractum Scillæ Fluidum.....	Fluidextractum Scillæ.
Extractum Scutellarariæ Fluidum.....	Fluidextractum Scutellarariæ.
Extractum Senegæ Fluidum.....	Fluidextractum Senegæ.
Extractum Sennæ Fluidum.....	Fluidextractum Sennæ.
Extractum Serpentariæ Fluidum.....	Fluidextractum Serpentariæ.
Extractum Spigeliæ Fluidum.....	Fluidextractum Spigeliæ.
Extractum Stillingiæ Fluidum.....	Fluidextractum Stillingiæ.
Extractum Taraxaci Fluidum.....	Fluidextractum Taraxaci.
Extractum Tritici Fluidum.....	Fluidextractum Tritici.
Extractum Uvæ Ursi Fluidum.....	Fluidextractum Uvæ Ursi.
Extractum Valerianæ Fluidum.....	Fluidextractum Valerianæ.
Extractum Veratri Viridis Fluidum.....	Fluidextractum Veratri.
Extractum Viburni Opuli Fluidum.....	Fluidextractum Viburni Opuli.
Extractum Viburni Prunifolii Fluidum.....	Fluidextractum Viburni Prunifolii.
Extractum Xanthoxyli Fluidum.....	Fluidextractum Xanthoxyli.
Extractum Zingiberis Fluidum.....	Fluidextractum Zingiberis.
Ferri Oxidum Hydratum.....	Ferri Hydroxidum.
Ferri Oxidum Hydratum cum Magnesia.....	Ferri Hydroxidum cum Magnesi Oxido.
Glyceritum Acidi Carbolicæ.....	Glyceritum Phenolis.
Gossypii Radicis Cortex.....	Gossypii Cortex.
Guaiaci Resina.....	Guaiacum.
Hamamelis.....	Hamamelidis Folia.
Hydrastininæ Hydrochloras.....	Hydrastininæ Hydrochloridum.

*Changes in official Latin titles of pharmacopœial preparations—Continued.*

Pharmacopœia, 1890.	Pharmacopœia, Eighth Revision.
Hyoscinae Hydrobromas.....	Hyoscinae Hydrobromidum.
Hyoscyaminae Hydrobromas .....	Hyoscyaminae Hydrobromidum.
Liquor Potassæ.....	Liquor Potassii Hydroxidi.
Liquor Sodæ.....	Liquor Sodii Hydroxidi.
Liquor Sodæ Chloratæ .....	Liquor Sodæ Chlorinatæ.
Magnesia.....	Magnesiæ Oxidum.
Magnesia Ponderosa.....	Magnesiæ Oxidum Ponderosum.
Mangani Dioxidum .....	Mangani Dioxidum Præcipitatum.
Mel Despumatam .....	Mel Depuratum.
Methyl Salicylas .....	Methylis Salicylas.
Morphinæ Hydrochloras .....	Morphinæ Hydrochloridum.
Naphthalinum.....	Naphthalenum.
Naphtol .....	Betanaphthol.
Oleum Betulæ Volatile.....	Oleum Betulæ.
Petrolatum Molle .....	Petrolatum.
Petrolatum Spissum.....	Petrolatum.
Phytolacœ Radix .....	Phytolacœa.
Pilocarpinæ Hydrochloras .....	Pilocarpinæ Hydrochloridum.
Potassa.....	Potassii Hydroxidum.
Potassi Bichromas.....	Potassii Dichromas.
Quercus Alba.....	Quercus.
Quininæ Hydrobromas.....	Quininæ Hydrobromidum.
Quininæ Hydrochloras.....	Quininæ Hydrochloridum.
Resorcinum .....	Resorcinol.
Salol.....	Phenylis Salicylas.
Sevum.....	Sevum Preparatum.
Soda.....	Sodii Hydroxidum.
Sodii Hyposulphis.....	Sodii Thiosulphas.
Sodii Sulphocarbolas.....	Sodii Phenolsulphonas.
Spiritus Glonoïni .....	Spiritus Glycerylis Nitratis.
Stramonii Folia .....	Stramonium.
Tinctura Arnicæ Florum.....	Tinctura Arnicæ.
Tinctura Stramonii Seminis.....	Tinctura Stramonii.
Tinctura Veratri Viridis.....	Tinctura Veratri.
Unguentum Acidi Carbolici.....	Unguentum Phenolis
Veratrum Viride .....	Veratrum.
Vinum Ferri Citratis .....	Vinum Ferri.
Zinci Valerianas.....	Zinci Valeras.

## ARTICLES DISMISSED FROM THE PHARMACOPŒIA.

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- Absinthium.  
 Acidum Carbolicum Crudum.  
 Alcohol Deodoratum.<sup>1</sup>  
 Allium.  
 Ammoniacum.  
 Ammonii Nitras.  
 Antimonii Oxidum.  
 Antimonii Sulphidum.  
 Antimonii Sulphidum Purificatum.  
 Antimonium Sulphuratum.  
 Argenti Iodidum.  
 Arnicæ Radix.<sup>2</sup>  
 Asclepias.  
 Aspidosperma.  
 Bari Dioxidum.<sup>3</sup>  
 Bryonia.  
 Cascarilla.  
 Castanea.  
 Catechu.<sup>4</sup>  
 Caulophyllum.  
 Ceratum Cetacei.  
 Cetraria.  
 Charta Potassii Nitratis.  
 Chelidonium.  
 Chenopodium.  
 Cinchonina.<sup>5</sup>  
 Cinnamomum Cassia.<sup>6</sup>  
 Crocus.  
 Decoetum Cetrariæ.  
 Decoetum Sarsaparillæ Compositum.  
 Dulcamara.  
 Elixir Phosphori.<sup>7</sup>  
 Emplastrum Ammoniaci cum Hydrargyro.  
 Emplastrum Arnicæ.  
 Emplastrum Ferri.  
 Emplastrum Ichthyocollæ.  
 Emplastrum Picis Burgundicæ.  
 Emplastrum Picis Cantharidatum.  
 Emplastrum Resinæ.<sup>8</sup>  
 Emulsum Ammoniaci.  
 Extractum Aconiti.<sup>9</sup>  
 Extractum Arnicæ Radicis.  
 Extractum Arnicæ Radicis Fluidum.  
 Extractum Asclepiadis Fluidum.  
 Extractum Aspidospermatis Fluidum.  
 Extractum Castanæe Fluidum.  
 Extractum Cinchonæ.  
 Extractum Colchici Radicis Fluidum.<sup>10</sup>  
 Extractum Conii.  
 Extractum Cusso Fluidum.  
 Extractum Dulcamaræ Fluidum.  
 Extractum Gossypii Radicis Fluidum.<sup>11</sup>  
 Extractum Iridis.  
 Extractum Iridis Fluidum.  
 Extractum Jalapæ.  
 Extractum Juglandis.  
 Extractum Lobeliæ Fluidum (hydro-alcoholic menstruum).<sup>12</sup>  
 Extractum Menispermii Fluidum.  
 Extractum Podophylli.  
 Extractum Rumeis Fluidum.  
 Extractum Sanguinariæ Fluidum (hydro-alcoholic menstruum).<sup>12</sup>  
 Extractum Scillæ Fluidum (hydro-alcoholic menstruum).<sup>12</sup>  
 Extractum Scoparii Fluidum.  
 Extractum Stramonii Seminis.<sup>13</sup>  
 Extractum Stramonii Seminis Fluidum.  
 Extractum Uvæ Ursi.  
 Ferri Iodidum Saccharatum.  
 Ferri Lactas.  
 Ferri Valerianas.  
 Glyceritum Vitelli.  
 Guaiaci Lignum.  
 Hydrargyri Cyanidum.  
 Hydrargyri Subsulphas Flavus.  
 Ichthyocolla.  
 Illicium.  
 Infusum Cinchonæ.  
 Inula.  
 Iris.  
 Juglans.  
 Kamala.  
 Linimentum Sinapis Compositum.  
 Liquor Ferri Acetatis.  
 Liquor Ferri Citratis.  
 Liquor Ferri Nitratis.  
 Liquor Sodii Silicatis.  
 Macis.  
 Magnesium Citras Effervescens.<sup>14</sup>  
 Massa Copaibæ.  
 Melissa.  
 Menispermum.  
 Oleatum Zinci.<sup>15</sup>  
 Oleum Aurantii Florum.<sup>16</sup>  
 Oleum Bergamottæ.  
 Oleum Myrciæ.  
 Oleum Phosphoratum.  
 Oleum Sesami.  
 Pepsinum Saccharatum.  
 Phytolacæ Fructus.<sup>17</sup>  
 Picrotoxinum.  
 Pilulæ Ales et Asafetidæ.  
 Pilulæ Antimonii Compositæ.  
 Pilulæ Rhei.  
 Pix Burgundica.  
 Plumbi Carbonas.  
 Potassa cum Calce.  
 Potassa Sulphurata.  
 Pulsatilla.



Pulyis Antimonialis.	Tinctura Arnicae Radicis.
Quinidinæ Sulphas.	Tinctura Bryoniae.
Quininæ Valerianas.	Tinctura Catechu Composita. <sup>21</sup>
Resina Copaibæ.	Tinctura Chiratae.
Rhus Toxicodendron.	Tinctura Croci.
Rosa Centifolia.	Tinctura Cubebæ.
Rubus Idæus.	Tinctura Humuli.
Rumex.	Tinctura Matico.
Sambucus.	Tinctura Rhei Dulcis.
Sodii Carbonas. <sup>18</sup>	Tinctura Stramonii Seminis. <sup>13</sup>
Sodii Carbonas Exsiccatus. <sup>18</sup>	Tinctura Sumbul. <sup>22</sup>
Spiritus Aurantii.	Trochisci Catechu. <sup>23</sup>
Spiritus Limonis. <sup>19</sup>	Trochisci Cretæ.
Spiritus Myrciæ.	Trochisci Ferri.
Spiritus Myristicæ.	Trochisci Ipecacuanhæ.
Spiritus Phosphori.	Trochisci Menthæ Piperitæ.
Stramonii Semen. <sup>13</sup>	Trochisci Morphinæ et Ipecacuanhæ.
Strontii Lactas.	Trochisci Zingiberis.
Syrupus Allii.	Unguentum Plumbi Carbonatis.
Syrupus Althææ.	Unguentum Plumbi Iodidi.
Syrupus Hypophosphitum cum Ferro. <sup>20</sup>	Unguentum Stramonii (seed). <sup>24</sup>
Syrupus Rubi Idæi.	Vinum Colchicæ Radicis. <sup>25</sup>
Tabacum.	Vitellus.
Tanacetum.	Zinci Phosphidum.

<sup>1</sup> The standard of Alcohol in the Eighth Revision has been raised, making it about equivalent to Alcohol Deodoratum (U. S. P., 1890).

<sup>2</sup> Arnicae Flores (U. S. P., 1890) becomes Arnica in the present revision.

<sup>3</sup> Never used in medicine; heretofore only in the preparation of Aqua Hydrogenii Dioxidii.

<sup>4</sup> Replaced by Gambir.

<sup>5</sup> Cinchoninæ Sulphas is retained.

<sup>6</sup> Saigon and Ceylon are retained, and Cinnamic Aldehyde, the most important constituent of Cinnamon, has been introduced.

<sup>7</sup> The Pills of Phosphorus are retained.

<sup>8</sup> Replaced by Emplastrum Adhæsivum.

<sup>9</sup> Alkaloid Aconitine introduced.

<sup>10</sup> Fluidextractum Colchici Seminis is retained, and Colchicine is introduced.

<sup>11</sup> Gossypii Radicis Cortex (1890) = Gossypii Cortex, Eighth Revision.

<sup>12</sup> The new Fluidextractum is a hydro-acetic acid extract.

<sup>13</sup> Stramonii Folia (1890) = Stramonium, Eighth Revision, of which there are an extract, a fluid-extract and a tincture. The present extract is made from the fluidextract.

<sup>14</sup> See Magnesii Sulphas Effervescens, page 45.

<sup>15</sup> See Zinci Stearas, page 61.

<sup>16</sup> Oleum Aurantii Corticis is retained.

<sup>17</sup> Phytolacæ Radix (1890) = Phytolacca, Eighth Revision.

<sup>18</sup> See Sodii Carbonas Monohydratus, page 53.

<sup>19</sup> Tinctura Limonis is introduced.

<sup>20</sup> See Syrupus Hypophosphitum Compositus, page 57.

<sup>21</sup> Replaced by Tinctura Gambir Composita.

<sup>22</sup> Fluidextractum Sumbul is introduced.

<sup>23</sup> Replaced by Trochisci Gambir.

<sup>24</sup> Made from Extractum Stramonii, Eighth Revision.

<sup>25</sup> Vinum Colchici Seminis is retained.

TABLE OF AVERAGE DOSES, AS GIVEN BY THE U. S.  
PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.

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The Pharmacopœial Convention of 1900 instructed the Committee of Revision "to state the average approximate (but neither a maximum nor a minimum) dose for adults, \* \* \* the metric system to be used, and the approximate equivalent ordinary weights or measures inserted in parentheses," and the Committee was further directed to make the following distinct declaration: "That neither this Convention, nor the Committee of Revision created by it, intends to have these doses regarded as obligatory on the physician or as forbidding him to exceed them whenever in his judgment this seems advisable."

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Acetanilidum .....	0. 250 Gm. = 250 milligrammes.		4 grains.
Acetphenetidinum .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Acetum Opii .....	0. 5 Cc.		8 minims.
Acetum Scillæ .....	1 Cc.		15 minims.
Acidum Aceticum Dilutum .....	2 Cc.		30 minims.
Acidum Benzoicum .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Acidum Boricum .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Acidum Camphoricum .....	1 Gm.		15 grains.
Acidum Citricum .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Acidum Gallicum .....	1 Gm.		15 grains.
Acidum Hydriodicum Dilutum .....	0. 5 Cc.		8 minims.
Acidum Hydrobromicum Dilutum .....	4 Cc.		1 fluidrachm.
Acidum Hydrochloricum Dilutum .....	1 Cc.		15 minims.
Acidum Hydrocyanicum Dilutum .....	0. 1 Cc.		1½ minims.
Acidum Hypophosphorosum Dilutum .....	0. 5 Cc.		8 minims.
Acidum Lacticum .....	2 Cc.		30 minims.
Acidum Nitricum Dilutum .....	2 Cc.		30 minims.
Acidum Nitrohydrochloricum .....	0. 2 Cc.		3 minims.
Acidum Nitrohydrochloricum Dilutum .....	1 Cc.		15 minims.
Acidum Phosphoricum Dilutum .....	2 Cc.		30 minims.

Table of average doses, as given by the U. S. Pharmacopœia, Eighth Decennial Revision—Continued.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Acidum Salicylicum .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Acidum Sulphuricum Aromaticum .....	1 Cc.		15 minims.
Acidum Sulphuricum Dilutum .....	2 Cc.		30 minims.
Acidum Sulphurosum .....	2 Cc.		30 minims.
Acidum Tannicum .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Acidum Tartaricum .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Aconitina .....	0. 00015 Gm. = 0. 15 milligramme.		$\frac{1}{100}$ grain.
Aconitum .....	0. 065 Gm. = 65 milligrammes.		1 grain.
Æther .....	1 Cc.		15 minims.
Æther Aceticus .....	1 Cc.		15 minims.
Æthylis Carbamas .....	1 Gm.		15 grains.
Aloe .....	0. 250 Gm. = 250 milligrammes.		4 grains.
Aloe Purificata .....	0. 250 Gm. = 250 milligrammes.		4 grains.
Alouinum .....	0. 065 Gm. = 65 milligrammes.		1 grain.
Alumen .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Ammonii Benzoas .....	1 Gm.		15 grains.
Ammonii Bromidum .....	1 Gm.		15 grains.
Ammonii Carbonas .....	0. 250 Gm. = 250 milligrammes.		4 grains.
Ammonii Chloridum .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Ammonii Iodidum .....	0. 250 Gm. = 250 milligrammes.		4 grains.



Ammonii Salicylas .....	0. 250 Gm. = 250 milligrammes.	4 grains.
Ammonii Valeras .....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Amylis Nitris .....	0. 2 Cc.	3 minims.
Anisum .....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Anthemis .....	2 Gm.	30 grains.
Antimonii et Potassii Tartras .....	0. 005 Gm. = 5 milligrammes.	⅓ grain.
.....	0. 030 Gm. = 30 milligrammes.	½ grain.
Antipyrina .....	0. 250 Gm. = 250 milligrammes.	4 grains.
Apocynum .....	1 Gm.	15 grains.
Apomorphinae Hydrochloridum .....	0. 002 Gm. = 2 milligrammes.	⅓ grain.
.....	0. 005 Gm. = 5 milligrammes.	⅓ grain.
Aqua Ammonia .....	1 Cc.	15 minims.
Aqua Amygdale Amare .....	4 Cc.	1 fluidrachm.
Aqua Anisi .....	16 Cc.	4 fluidrachms.
Aqua Aurantii Florum .....	16 Cc.	4 fluidrachms.
Aqua Aurantii Florum Fortior .....	8 Cc.	2 fluidrachms.
Aqua Camphore .....	8 Cc.	2 fluidrachms.
Aqua Chloroformi .....	16 Cc.	4 fluidrachms.
Aqua Cinnamomi .....	16 Cc.	4 fluidrachms.
Aqua Creosoti .....	8 Cc.	2 fluidrachms.
Aqua Foeniculi .....	16 Cc.	4 fluidrachms.
Aqua Hamamelidis .....	8 Cc.	2 fluidrachms.
Aqua Hydrogenii Dioxidi .....	4 Cc.	1 fluidrachm.
Aqua Menthae Piperite .....	16 Cc.	4 fluidrachms.
Aqua Menthae Viridis .....	16 Cc.	4 fluidrachms.
Aqua Rose .....	16 Cc.	4 fluidrachms.

Table of average doses, as given by the U. S. Pharmacopœia, Eighth Decennial Revision—Continued.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Aqua Rosæ Fortior.....	8 Cc.		2 fluidrachms.
Argenti Nitras.....	0.010 Gm. = 10 milligrammes.		$\frac{1}{3}$ grain.
Argenti Oxidum.....	0.065 Gm. = 65 milligrammes.		1 grain.
Arnica.....	1 Gm.		15 grains.
Arseni Iodidum.....	0.005 Gm. = 5 milligrammes.		$\frac{1}{10}$ grain.
Arseni Trioxidum.....	0.002 Gm. = 2 milligrammes.		$\frac{1}{30}$ grain.
Asafoetida.....	0.250 Gm. = 250 milligrammes.		4 grains.
Aspidium.....	4 Gm.		60 grains.
Atropina.....	0.0004 Gm. = 0.4 milligramme.		$\frac{1}{100}$ grain.
Atropinæ Sulphas.....	0.0004 Gm. = 0.4 milligramme.		$\frac{1}{100}$ grain.
Aurantii Amari Cortex.....	1 Gm.		15 grains.
Aurantii Dulcis Cortex.....	1 Gm.		15 grains.
Auri et Sodii Chloridum.....	0.005 Gm. = 5 milligrammes.		$\frac{1}{10}$ grain.
Balsamum Peruvianum.....	1 Gm.		15 grains.
Balsamum Tolutanum.....	1 Gm.		15 grains.
Belladonnæ Folia.....	0.065 Gm. = 65 milligrammes.		1 grain.
Belladonnæ Radix.....	0.045 Gm. = 45 milligrammes.		$\frac{3}{4}$ grain.
Benzaldehydum.....	0.03 Cc.		$\frac{1}{2}$ minim.
Benzoinum.....	1 Gm.		15 grains.
Benzosulphinidum.....	0.200 Gm. = 200 milligrammes.		3 grains.

Berberis.....	2 Gm.	30 grains.
Betanaphthol.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Bismuthi Citras.....	0. 125 Gm. = 125 milligrammes.	2 grains.
Bismuthi et Ammonii Citras.....	0. 125 Gm. = 125 milligrammes.	2 grains.
Bismuthi Subcarbonas.....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Bismuthi Subgallas.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Bismuthi Subnitras.....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Bismuthi Subsalicylas.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Bronoformum.....	0. 2 Cc.	3 minims.
Buchu.....	2 Gm.	30 grains.
Caffeina.....	0. 065 Gm. = 65 milligrammes.	1 grain.
Caffeina Citrata.....	0. 125 Gm. = 125 milligrammes.	2 grains.
Caffeina Citrata Effervescens.....	4 Gm.	60 grains.
Calamus.....	1 Gm.	15 grains.
Calcii Bromidum.....	1 Gm.	15 grains.
Calcii Carbonas Præcipitatus.....	1 Gm.	15 grains.
Calcii Chloridum.....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Calcii Hypophosphis.....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Calcii Phosphas Præcipitatus.....	1 Gm.	15 grains.
Calendula.....	1 Gm.	15 grains.
Calumba.....	2 Gm.	30 grains.
Calx Chlorinata.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Calx Sulphurata.....	0. 065 Gm. = 65 milligrammes.	1 grain.
Cambogia.....	0. 125 Gm. = 125 milligrammes.	2 grains.
Camphora.....	0. 125 Gm. = 125 milligrammes.	2 grains.
Camphora Monobromata.....	0. 125 Gm. = 125 milligrammes.	2 grains.

Table of average doses, as given by the U. S. Pharmacopœia, Eighth Decennial Revision—Continued.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Cannabis Indica .....	0.065 Gm. = 65 milligrammes.		1 grain.
Cantharis .....	0.030 Gm. = 30 milligrammes.		½ grain.
Capsicum .....	0.065 Gm. = 65 milligrammes.		1 grain.
Carbo Ligni .....	1 Gm.		15 grains.
Cardamomum .....	1 Gm.		15 grains.
Carum .....	1 Gm.		15 grains.
Caryophyllus .....	0.250 Gm. = 250 milligrammes.		4 grains.
Cassia Fistula .....	4 Gm.		60 grains.
Cerii Oxalas .....	0.065 Gm. = 65 milligrammes.		1 grain.
Chinaphila .....	2 Gm.		30 grains.
Chirata .....	1 Gm.		15 grains.
Chloroformamidum .....	1 Gm.		15 grains.
Chloralum Hydratum .....	1 Gm.		15 grains.
Chloroformum .....	0.3 Cc.		5 minims.
Chondrus .....	15 Gm.		4 drachms.
Chrysarobinum .....	0.030 Gm. = 30 milligrammes.		½ grain.
Cimicifuga .....	1 Gm.		15 grains.
Cinchona .....	1 Gm.		15 grains.
Cinchona Rubra .....	1 Gm.		15 grains.
Cinchonidinæ Sulphas .....	0.250 Gm. = 250 milligrammes.		4 grains.

In decoction.



Cinchoninæ Sulphas.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Cinnaldehydum.....	0. 05 Cc.	1 minim.
Cinnamomum Saigonicum.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Cinnamomum Zeylanicum.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Coca.....	2 Gm.	30 grains.
Cocaina.....	0. 030 Gm. = 30 milligrammes.	½ grain.
Cocainæ Hydrochloridum.....	0. 030 Gm. = 30 milligrammes.	½ grain.
Codeina.....	0. 030 Gm. = 30 milligrammes.	½ grain.
Codeinæ Phosphas.....	0. 030 Gm. = 30 milligrammes.	½ grain.
Codeinæ Sulphas.....	0. 030 Gm. = 30 milligrammes.	½ grain.
Colchici Cormus.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Colchici Semen.....	0. 200 Gm. = 200 milligrammes.	3 grains.
Colchicina.....	0. 0005 Gm. = 0.5 milligrammes.	1½ grain.
Colocyntthis.....	0. 065 Gm. = 65 milligrammes.	1 grain.
Confectio Sennæ.....	4 Gm.	60 grains.
Conium.....	0. 200 Gm. = 200 milligrammes.	3 grains.
Convallaria.....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Copaiba.....	1 Cc.	15 minims.
Coriandrum.....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Creosotum.....	0. 2 Cc.	3 minims.
Cresol.....	0. 05 Cc.	1 minim.
Creta Preparata.....	1 Gm.	15 grains.
Cubeba.....	1 Gm.	15 grains.
Cupri Sulphas.....	0. 010 Gm. = 10 milligrammes.	½ grain.
.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Cusso.....	16 Gm.	240 grains.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Cypripedium .....	1 Gm.		15 grains.
Digitalis .....	0.065 Gm. = 65 milligrammes.		1 grain.
Elatarium .....	0.005 Gm. = 5 milligrammes.		$\frac{1}{16}$ grain.
Elixir Ferri, Quininae, et Strychninae Phosphatum .....	4 Cc.		1 fluidrachm.
Emulsium Amygdalæ .....	120 Cc.		4 fluidounces.
Emulsium Asafetidae .....	16 Cc.		4 fluidrachms.
Emulsium Chloroformi .....	8 Cc.		2 fluidrachms.
Emulsium Olei Morrhuae .....	8 Cc.		2 fluidrachms.
Emulsium Olei Morrhuae cum Hypophosphitibus .....	8 Cc.		2 fluidrachms.
Emulsium Olei Terebinthinae .....	4 Cc.		1 fluidrachm.
Ergota .....	2 Gm.		30 grains.
Eriodictyon .....	1 Gm.		15 grains.
Eucalyptol .....	0.3 Cc.		5 minims.
Eucalyptus .....	2 Gm.		30 grains.
Eugenol .....	0.2 Cc.		3 minims.
Eunymus .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Eupatorium .....	2 Gm.		30 grains.
Extractum Aloes .....	0.125 Gm. = 125 milligrammes.		2 grains.
Extractum Belladonnae Foliorum .....	0.010 Gm. = 10 milligrammes.		$\frac{1}{8}$ grain.
Extractum Cannabis Indicae .....	0.010 Gm. = 10 milligrammes		$\frac{1}{8}$ grain.

Extractum Cimicifugæ.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Extractum Colechici Corni.....	0. 065 Gm. = 65 milligrammes.	1 grain.
Extractum Colocynthis.....	0. 030 Gm. = 30 milligrammes.	$\frac{1}{2}$ grain.
Extractum Colocynthis Compositum.....	0. 500 Gm. = 500 milligrammes.	7 $\frac{1}{2}$ grains.
Extractum Digitalis.....	0. 010 Gm. = 10 milligrammes.	$\frac{1}{2}$ grain.
Extractum Ergotæ.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Extractum Euonymi.....	0. 125 Gm. = 125 milligrammes.	2 grains.
Extractum Gentianæ.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Extractum Glycyrrhizæ.....	1 Gm.	15 grains.
Extractum Glycyrrhizæ Purum.....	1 Gm.	15 grains.
Extractum Hamatoxyli.....	1 Gm.	15 grains.
Extractum Hyoscyami.....	0. 065 Gm. = 65 milligrammes.	1 grain.
Extractum Kramerie.....	0. 500 Gm. = 500 milligrammes.	7 $\frac{1}{2}$ grains.
Extractum Leptandree.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Extractum Malti.....	16 Cc.	4 fluidrachms.
Extractum Nucis Vomice.....	0. 015 Gm. = 15 milligrammes.	$\frac{1}{4}$ grain.
Extractum Opii.....	0. 030 Gm. = 30 milligrammes.	$\frac{1}{2}$ grain.
Extractum Physostigmatis.....	0. 008 Gm. = 8 milligrammes.	$\frac{1}{8}$ grain.
Extractum Quassie.....	0. 065 Gm. = 65 milligrammes.	1 grain.
Extractum Rhamni Purshianæ.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Extractum Rhei.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Extractum Scopolæ.....	0. 010 Gm. = 10 milligrammes.	$\frac{1}{2}$ grain.
Extractum Stramonii.....	0. 010 Gm. = 10 milligrammes.	$\frac{1}{2}$ grain.
Extractum Sumbul.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Extractum Taraxaci.....	1 Gm.	15 grains.
Fel Bovis Purificatum.....	0. 500 Gm. = 500 milligrammes.	7 $\frac{1}{2}$ grains.

Table of average doses, as given by the U. S. Pharmacopœia, Eighth Decennial Revision—Continued.

PREPARATION.	AVERAGE DOSE.	Approximate Equivalent Ordinary System.
	Metric System.	
Ferri Carbonas Saccharatus.....	0.250 Gm. = 250 milligrammes.	4 grains.
Ferri Chloridum.....	0.065 Gm. = 65 milligrammes.	1 grain.
Ferri Citras.....	0.250 Gm. = 250 milligrammes.	4 grains.
Ferri et Ammonii Citras.....	0.250 Gm. = 250 milligrammes.	4 grains.
Ferri et Ammonii Sulphas.....	0.500 Gm. = 500 milligrammes.	7½ grains.
Ferri et Ammonii Tartas.....	0.250 Gm. = 250 milligrammes.	4 grains.
Ferri et Potassii Tartas.....	0.250 Gm. = 250 milligrammes.	4 grains.
Ferri et Quininae Citras.....	0.250 Gm. = 250 milligrammes.	4 grains.
Ferri et Quininae Citras Solubilis.....	0.250 Gm. = 250 milligrammes.	4 grains.
Ferri et Strychninae Citras.....	0.125 Gm. = 125 milligrammes.	2 grains.
Ferri Hydroxidum cum Magnesii Oxido.....	120 Cc.	4 fluidounces.
Ferri Hypophosphis.....	0.200 Gm. = 200 milligrammes.	3 grains.
Ferri Phosphas Solubilis.....	0.250 Gm. = 250 milligrammes.	4 grains.
Ferri Pyrophosphas Solubilis.....	0.250 Gm. = 250 milligrammes.	4 grains.
Ferri Sulphas.....	0.200 Gm. = 200 milligrammes.	3 grains.
Ferri Sulphas Exsiccatus.....	0.125 Gm. = 125 milligrammes.	2 grains.
Ferri Sulphas Granulatus.....	0.200 Gm. = 200 milligrammes.	3 grains.
Ferrum Reductum.....	0.065 Gm. = 65 milligrammes.	1 grain.
Fluidextractum Aconiti.....	0.05 Cc.	1 minim.
Fluidextractum Apocyni.....	1 Cc.	15 minims.



Fluidextractum Aromaticum.....	1 Cc.	15 minims.
Fluidextractum Aurantii Amari.....	1 Cc.	15 minims.
Fluidextractum Belladonnae Radicis.....	0.05 Cc.	1 minim.
Fluidextractum Berberidis.....	2 Cc.	30 minims.
Fluidextractum Buchu.....	2 Cc.	30 minims.
Fluidextractum Calami.....	1 Cc.	15 minims.
Fluidextractum Calumbae.....	2 Cc.	30 minims.
Fluidextractum Cannabis Indicae.....	0.05 Cc.	1 minim.
Fluidextractum Capsici.....	0.05 Cc.	1 minim.
Fluidextractum Chimaphilae.....	2 Cc.	30 minims.
Fluidextractum Chiratae.....	1 Cc.	15 minims.
Fluidextractum Cimicifugae.....	1 Cc.	15 minims.
Fluidextractum Cinchonae.....	1 Cc.	15 minims.
Fluidextractum Cocae.....	2 Cc.	30 minims.
Fluidextractum Colchici Seminis.....	0.2 Cc.	3 minims.
Fluidextractum Conii.....	0.2 Cc.	3 minims.
Fluidextractum Convallariae.....	0.5 Cc.	8 minims.
Fluidextractum Cubebae.....	1 Cc.	15 minims.
Fluidextractum Cypripedii.....	1 Cc.	15 minims.
Fluidextractum Digitalis.....	0.05 Cc.	1 minim.
Fluidextractum Ergotae.....	2 Cc.	30 minims.
Fluidextractum Eriodictyi.....	1 Cc.	15 minims.
Fluidextractum Eucalypti.....	2 Cc.	30 minims.
Fluidextractum Eponymii.....	0.5 Cc.	8 minims.
Fluidextractum Eupatorii.....	2 Cc.	30 minims.
Fluidextractum Frangulae.....	1 Cc.	15 minims.

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Fluidextractum Gelsemii .....	0.05 Cc.	1 minim.
Fluidextractum Gentiane .....	1 Cc.	15 minims.
Fluidextractum Geranii .....	1 Cc.	15 minims.
Fluidextractum Glycyrrhizæ .....	2 Cc.	30 minims.
Fluidextractum Granati .....	2 Cc.	30 minims.
Fluidextractum Grindeliæ .....	2 Cc.	30 minims.
Fluidextractum Guaraniæ .....	2 Cc.	30 minims.
Fluidextractum Hamamelidis Foliorum .....	2 Cc.	30 minims.
Fluidextractum Hydrastis .....	2 Cc.	30 minims.
Fluidextractum Hyoscyami .....	0.2 Cc.	3 minims.
Fluidextractum Ipecacuanhæ .....	1 Cc.	15 minims.
Fluidextractum Krameriæ .....	0.05 Cc.	1 minim.
Fluidextractum Lappæ .....	1 Cc.	15 minims.
Fluidextractum Leptandree .....	2 Cc.	30 minims.
Fluidextractum Lobeliæ .....	1 Cc.	15 minims.
Fluidextractum Lupulini .....	0.5 Cc.	8 minims.
Fluidextractum Matico .....	0.5 Cc.	8 minims.
Fluidextractum Nucis Vomiciæ .....	4 Cc.	1 fluidrachm.
Fluidextractum Pareire .....	0.05 Cc.	1 minim.
Fluidextractum Pareire .....	2 Cc.	30 minims.

} Emetic  
{ Expectorant

	{ Emetic Alterative }	
Fluidextractum Phytolaccae.....		1 Cc.
Fluidextractum Pilocarpi.....		0. 1 Cc.
Fluidextractum Podophylli.....		2 Cc.
Fluidextractum Pruni Virginianae.....		0. 5 Cc.
Fluidextractum Quassiae.....		2 Cc.
Fluidextractum Quercus.....		0. 5 Cc.
Fluidextractum Quillajae.....		1 Cc.
Fluidextractum Rhamni Purshianae.....		0. 2 Cc.
Fluidextractum Rhamni Purshianae Aromaticum.....		1 Cc.
Fluidextractum Rhei.....		1 Cc.
Fluidextractum Rhois Glabrae.....		1 Cc.
Fluidextractum Rose.....		2 Cc.
Fluidextractum Rubi.....		1 Cc.
Fluidextractum Sabineae.....		0. 3 Cc.
Fluidextractum Sanguinariae.....		0. 1 Cc.
Fluidextractum Sarsaparillae.....		2 Cc.
Fluidextractum Sarsaparillae Compositum.....		2 Cc.
Fluidextractum Scilliae.....		0. 1 Cc.
Fluidextractum Scopolae.....		0. 05 Cc.
Fluidextractum Scutellariae.....		1 Cc.
Fluidextractum Senegae.....		1 Cc.
Fluidextractum Sennae.....		2 Cc.
Fluidextractum Serpentariae.....		1 Cc.
Fluidextractum Spigeliae.....		4 Cc.
Fluidextractum Staphisagriae.....		0. 05 Cc.

15 minims.
1½ minims.
30 minims.
8 minims.
30 minims.
8 minims.
15 minims.
3 minims.
15 minims.
15 minims.
15 minims.
15 minims.
30 minims.
15 minims.
5 minims.
1½ minims.
30 minims.
30 minims.
1½ minims.
1 minim.
15 minims.
15 minims.
30 minims.
15 minims.
1 fluidrachm.
1 minim.

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Fluidextractum Stillingie.....	2 Cc.	30 minims.
Fluidextractum Stramonii.....	0.05 Cc.	1 minim.
Fluidextractum Sumbul.....	2 Cc.	30 minims.
Fluidextractum Taxacaci.....	8 Cc.	2 fluidrachms.
Fluidextractum Tritici.....	8 Cc.	2 fluidrachms.
Fluidextractum Uvae Ursi.....	2 Cc.	30 minims.
Fluidextractum Valerianæ.....	2 Cc.	30 minims.
Fluidextractum Veratri.....	0.1 Cc.	1½ minims.
Fluidextractum Viburni Opuli.....	2 Cc.	30 minims.
Fluidextractum Viburni Prunifolii.....	2 Cc.	30 minims.
Fluidextractum Xanthoxyli.....	2 Cc.	30 minims.
Fluidextractum Zingiberis.....	1 Cc.	15 minims.
Feniculum.....	1 Gm.	15 grains.
Frangula.....	1 Gm.	15 grains.
Galla.....	0.500 Gm. = 500 milligrammes.	7½ grains.
Gambir.....	1 Gm.	15 grains.
Gelsemium.....	0.065 Gm. = 65 milligrammes.	1 grain.
Gentiana.....	1 Gm.	15 grains.
Geranium.....	1 Gm.	15 grains.
Glandule Suprarenales Siccae.....	0.250 Gm. = 250 milligrammes.	4 grains.



Glandulae Thyroideae Siccae .....	0. 250 Gm. = 250 milligrammes.	4 grains.
Glycerinum .....	4 Cc.	1 fluidrachm.
Glyceritum Acidi Tannici .....	2 Cc.	30 minims.
Glyceritum Ferri, Quininae, et Strychninae Phosphatum .....	1 Cc.	15 minims.
Glyceritum Hydrastis .....	2 Cc.	30 minims.
Glyceritum Phenolis .....	0. 3 Cc.	5 minims.
Glycyrrhiza .....	2 Gm.	30 grains.
Glycyrrhizinam Ammoniatam .....	0. 250 Gm. = 250 milligrammes.	4 grains.
Gossypii Cortex .....	2 Gm.	30 grains.
Granatum .....	2 Gm.	30 grains.
Grindelia .....	2 Gm.	30 grains.
Guaiacol .....	0. 5 Cc.	8 minims.
Guaiacolis Carbonas .....	1 Gm.	15 grains.
Guaiacum .....	1 Gm.	15 grains.
Guarana .....	2 Gm.	30 grains.
Hamamelidis Cortex .....	2 Gm.	30 grains.
Hamamelidis Folia .....	2 Gm.	30 grains.
Hedeoma .....	8 Gm.	120 grains.
Hexamethylenamina .....	0. 250 Gm. = 250 milligrammes.	4 grains.
Homatropinae Hydrobromidum .....	0. 0005 Gm. = 0. 5 milligramme.	$\frac{1}{128}$ grain.
Humulus .....	2 Gm.	30 grains.
Hydargyri Chloridum Corrosivum .....	0. 003 Gm. = 3 milligrammes.	$\frac{1}{30}$ grain.
Hydargyri Chloridum Mite .....	0. 125 Gm. = 125 milligrammes.	2 grains.
Hydargyri Iodidum Flavum .....	0. 065 Gm. = 65 milligrammes.	1 grain.
Hydargyri Iodidum Rubrum .....	0. 010 Gm. = 10 milligrammes.	$\frac{1}{5}$ grain.
	0. 003 Gm. = 3 milligrammes.	$\frac{1}{30}$ grain.

{ Laxative  
{ Alternative.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Hydrargyrum cum Creta.....	0. 250 Gm. = 250 milligrammes.		4 grains.
Hydrastina.....	0. 010 Gm. = 10 milligrammes.		$\frac{1}{2}$ grain.
Hydrastininae Hydrochloridum.....	0. 030 Gm. = 30 milligrammes.		$\frac{1}{2}$ grain.
Hydrastis.....	2 Gm.		30 grains.
Hyoscinæ Hydrobromidum.....	0. 0005 Gm. = 0. 5 milligramme.		$\frac{1}{128}$ grain.
Hyosyaminæ Hydrobromidum.....	0. 0005 Gm. = 0. 5 milligramme.		$\frac{1}{32}$ grain.
Hyosyaminæ Sulphas.....	0. 0005 Gm. = 0. 5 milligramme.		$\frac{1}{32}$ grain.
Hyoscyamus.....	0. 250 Gm. = 250 milligrammes.		4 grains.
Infusum Digitalis.....	8 Cc.		2 fluidrachms.
Infusum Pruni Virginianæ.....	60 Cc.		2 fluidounces.
Infusum Sennæ Compositum.....	120 Cc.		4 fluidounces.
Iodoformum.....	0. 250 Gm. = 250 milligrammes.		4 grains.
Iodolum.....	0. 250 Gm. = 250 milligrammes.		4 grains.
Iodum.....	0. 005 Gm. = 5 milligrammes.		$\frac{1}{16}$ grain.
Ipecacuanha.....	0. 065 Gm. = 65 milligrammes.		1 grain.
{ Expectorant.....	1 Gm.		15 grains.
{ Emetic.....	1 Gm.		15 grains.
Jalapa.....	0. 500 Gm. = 500 milligrammes.		7 $\frac{1}{2}$ grains.
Kino.....	1 Gm.		15 grains.
Krameria.....	1 Gm.		15 grains.
Lactucarium.....	1 Gm.		15 grains.

Lappa.....	2 Gm.	30 grains.
Leptandra.....	1 Gm.	15 grains.
Limonis Succus.....	30 Cc.	1 fluidounce.
Liquor Acidi Arsenosi.....	0.2 Cc.	3 minims.
Liquor Ammonii Acetatis.....	16 Cc.	4 fluidrachms.
Liquor Antisepticus.....	4 Cc.	1 fluidrachm.
Liquor Arseni et Hydrargyri Iodidi.....	0.1 Cc.	1½ minims.
Liquor Calcis.....	16 Cc.	4 fluidrachms.
Liquor Chlori Compositus.....	4 Cc.	1 fluidrachm.
Liquor Ferri Chloridi.....	0.1 Cc.	1½ minims.
Liquor Ferri et Ammonii Acetatis.....	16 Cc.	4 fluidrachms.
Liquor Ferri Subsulphatis.....	0.2 Cc.	3 minims.
Liquor Iodi Compositus.....	0.2 Cc.	3 minims.
Liquor Magnesii Citratis.....	360 Cc.	12 fluidounces.
Liquor Potassii Arsenitis.....	0.2 Cc.	3 minims.
Liquor Potassii Citratis.....	16 Cc.	4 fluidrachms.
Liquor Potassii Hydroxidi.....	1 Cc.	15 minims.
Liquor Sodæ Chlorinate.....	1 Cc.	15 minims.
Liquor Sodii Arsenatis.....	0.2 Cc.	3 minims.
Liquor Sodii Hydroxidi.....	1 Cc.	15 minims.
Liquor Sodii Phosphatis Compositus.....	8 Cc.	2 fluidrachms.
Lithii Benzoes.....	1 Gm.	15 grains.
Lithii Bromidum.....	1 Gm.	15 grains.
Lithii Carbonas.....	0.560 Gm. = 500 milligrammes.	7½ grains.
Lithii Citras.....	0.500 Gm. = 500 milligrammes.	7½ grains.
Lithii Citras Effervescens.....	8 Gm.	120 grains.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Lithii Salicylas .....	1 Gm.		15 grains.
Lobelia.....	0.500 Gm. = 500 milligrammes.		7½ grains.
Lupulinum .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Magnesii Carbonas .....	3 Gm.		45 grains.
Magnesii Oxidum .....	2 Gm.		30 grains.
Magnesii Oxidum Ponderosum .....	2 Gm.		30 grains.
Magnesii Sulphas .....	16 Gm.		240 grains.
Magnesii Sulphas Effervescens .....	16 Gm.		240 grains.
Mangani Dioxidum Precipitatum .....	0.250 Gm. = 250 milligrammes.		4 grains.
Mangani Hypophosphis .....	0.200 Gm. = 200 milligrammes.		3 grains.
Mangani Sulphas.....	0.250 Gm. = 250 milligrammes.		4 grains.
Manna .....	16 Gm.		240 grains.
Marrubium .....	2 Gm.		30 grains.
Massa Ferri Carbonatis .....	0.250 Gm. = 250 milligrammes.		4 grains.
Massa Hydrargyri.....	0.250 Gm. = 250 milligrammes.		4 grains.
Mastiche .....	2 Gm.		30 grains.
Matico .....	4 Gm.		60 grains.
Matricaria .....	16 Gm.		240 grains.
Mel .....	4 Cc.		1 fluidrachm.
Mel Depuratum .....	4 Cc.		1 fluidrachm.



Mel Rose.....	4 Cc.	1 fluidrachm.
Mentha Piperita.....	4 Gm.	60 grains.
Mentha Viridis.....	4 Gm.	60 grains.
Menthol.....	0.065 Gm. = 65 milligrammes.	1 grain.
Methylis Salicylas.....	1 Cc.	15 minims.
Methylthionine Hydrochloridum.....	0.250 Gm. = 250 milligrammes.	4 grains.
Mezereum.....	0.500 Gm. = 500 milligrammes.	7½ grains.
Mistura Crete.....	16 Cc.	4 fluidrachms.
Mistura Ferri Composita.....	16 Cc.	4 fluidrachms.
Mistura Glycyrrhizæ Composita.....	8 Cc.	2 fluidrachms.
Mistura Rhei et Sodæ.....	4 Cc.	1 fluidrachm.
Morphina.....	0.010 Gm. = 10 milligrammes.	½ grain.
Morphinæ Acetas.....	0.015 Gm. = 15 milligrammes.	¼ grain.
Morphinæ Hydrochloridum.....	0.015 Gm. = 15 milligrammes.	¼ grain.
Morphinæ Sulphas.....	0.015 Gm. = 15 milligrammes.	¼ grain.
Moschus.....	0.250 Gm. = 250 milligrammes.	4 grains.
Mucilago Acaciæ.....	16 Cc.	4 fluidrachms.
Mucilago Sassafras Medullæ.....	16 Cc.	4 fluidrachms.
Mucilago Tragacanthæ.....	16 Cc.	4 fluidrachms.
Mucilago Ulmi.....	16 Cc.	4 fluidrachms.
Myristica.....	0.500 Gm. = 500 milligrammes.	7½ grains.
Myrrha.....	0.500 Gm. = 500 milligrammes.	7½ grains.
Naphthalenum.....	0.125 Gm. = 125 milligrammes.	2 grains.
Nux Vomica.....	0.065 Gm. = 65 milligrammes.	1 grain.
Oleoresina Aspidii.....	2 Gm.	30 grains.
Oleoresina Capsici.....	0.030 Gm. = 30 milligrammes.	½ grain.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Oleoresina Cubebe .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Oleoresina Lupulini .....	0.200 Gm. = 200 milligrammes.		3 grains.
Oleoresina Piperis .....	0.030 Gm. = 30 milligrammes.		½ grain.
Oleoresina Zingiberis .....	0.030 Gm. = 30 milligrammes.		½ grain.
Oleum Amygdalæ Amaræ .....	0.03 Cc.		½ minim.
Oleum Amygdalæ Expressum .....	30 Cc.		1 fluidounce.
Oleum Anisi .....	0.2 Cc.		3 minims.
Oleum Aurantii Corticis .....	0.2 Cc.		3 minims.
Oleum Betule .....	1 Cc.		15 minims.
Oleum Cajuputi .....	0.5 Cc.		8 minims.
Oleum Cari .....	0.2 Cc.		3 minims.
Oleum Caryophylli .....	0.2 Cc.		3 minims.
Oleum Chenopodii .....	0.2 Cc.		3 minims.
Oleum Cinnamomi .....	0.05 Cc.		1 minim.
Oleum Copaibæ .....	0.5 Cc.		8 minims.
Oleum Coriandri .....	0.2 Cc.		3 minims.
Oleum Cubebæ .....	0.5 Cc.		8 minims.
Oleum Erigerontis .....	1 Cc.		15 minims.
Oleum Eucalypti .....	0.5 Cc.		8 minims.
Oleum Fœniculi .....	0.2 Cc.		3 minims.

Oleum Gaultheriæ .....	1 Cc.	15 minims.
Oleum Gossypii Seminis .....	16 Cc.	4 fluidrachms.
Oleum Hedeomæ .....	0.2 Cc.	3 minims.
Oleum Juniperi .....	0.2 Cc.	3 minims.
Oleum Lavandulæ Florum .....	0.2 Cc.	3 minims.
Oleum Limonis .....	0.2 Cc.	3 minims.
Oleum Lini .....	30 Cc.	1 fluidounce.
Oleum Menthæ Piperitæ .....	0.2 Cc.	3 minims.
Oleum Menthæ Viridis .....	0.2 Cc.	3 minims.
Oleum Morrhuæ .....	16 Cc.	4 fluidrachms.
Oleum Myristicæ .....	0.2 Cc.	3 minims.
Oleum Olivæ .....	30 Cc.	1 fluidounce.
Oleum Picis Liquidæ .....	0.2 Cc.	3 minims.
Oleum Pimentæ .....	0.2 Cc.	3 minims.
Oleum Ricini .....	16 Cc.	4 fluidrachms.
Oleum Rosmarini .....	0.2 Cc.	3 minims.
Oleum Sabinæ .....	0.05 Cc.	1 minim.
Oleum Santali .....	0.5 Cc.	8 minims.
Oleum Sassafras .....	0.2 Cc.	3 minims.
Oleum Sinapis Volatile .....	0.008 Cc.	$\frac{1}{8}$ minim.
Oleum Terebinthinæ Rectificatum .....	1 Cc.	15 minims.
Oleum Thymi .....	0.2 Cc.	3 minims.
Oleum Tigli .....	0.05 Cc.	1 minim.
Opii Pulvis .....	0.065 Gm. = 65 milligrammes.	1 grain.
Opium .....	0.100 Gm. = 100 milligrammes.	$1\frac{1}{2}$ grains.
Opium Deodoratum .....	0.065 Gm. = 65 milligrammes.	1 grain.

Table of average doses, as given by the U. S. Pharmacopœia, Eighth Decennial Revision—Continued.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Opium Granulatum .....	0.065 Gm. = 65 milligrammes.		1 grain.
Pancreatinum .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Paraldehydum .....	2 Cc.		30 minims.
Pareira .....	2 Gm.		30 grains.
Pelletierinæ Tannas .....	0.250 Gm. = 250 milligrammes.		4 grains.
Pepo .....	30 Gm.		1 ounce.
Pepsinum .....	0.250 Gm. = 250 milligrammes.		4 grains.
Phenol .....	0.065 Gm. = 65 milligrammes.		1 grain.
Phenol Liquefactum .....	0.05 Cc.		1 minim.
Phenylis Salicylas .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Phosphorus .....	0.0005 Gm. = 0.5 milligramme.		⅙ grain.
Physostigma .....	0.100 Gm. = 100 milligrammes.		1½ grains.
Physostigminae Salicylas .....	0.001 Gm. = 1 milligramme.		⅙ grain.
Physostigminae Sulphas .....	0.001 Gm. = 1 milligramme.		⅙ grain.
Phytolacca .....	1 Gm.		15 grains.
	{ Emetic		
	{ Alterative .....		
Pilocarpinae Hydrochloridum .....	0.125 Gm. = 125 milligrammes.		2 grains.
Pilocarpinae Nitras .....	0.010 Gm. = 10 milligrammes.		⅓ grain.
Pilocarpus .....	0.010 Gm. = 10 milligrammes.		⅓ grain.
Pilulæ Aloes .....	2 Gm.		30 grains.
			2 pills.



Pilulæ Aloes et Ferri .....	2 pills.		
Pilulæ Aloes et Mastiches .....	2 pills.		
Pilulæ Aloes et Myrrhæ .....	2 pills.		
Pilulæ Asafoetidæ .....	2 pills.		
Pilulæ Cathartice Composite .....	2 pills.		
Pilulæ Cathartice Vegetabiles .....	2 pills.		
Pilulæ Ferri Carbonatis .....	2 pills.		
Pilulæ Ferri Iodidi .....	2 pills.		
Pilulæ Laxativæ Composite .....	2 pills.		
Pilulæ Opii .....	1 pill.		
Pilulæ Phosphori .....	1 pill.		
Pilulæ Podophylli, Belladonnæ et Capsici .....	1 pill.		
Pilulæ Rhei Composite .....	2 pills.		
Pimenta .....	1 Gm.		15 grains.
Piper .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Piperina .....	0. 200 Gm. = 200 milligrammes.		3 grains.
Pix Liquida .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Plumbi Acetas .....	0. 065 Gm. = 65 milligrammes.		1 grain.
Podophyllum .....	0. 500 Gm. = 500 milligrammes.		7½ grains.
Potassii Acetas .....	2 Gm.		30 grains.
Potassii Bicarbonas .....	2 Gm.		30 grains.
Potassii Bitartras .....	2 Gm.		30 grains.
Potassii Bromidum .....	1 Gm.		15 grains.
Potassii Carbonas .....	1 Gm.		15 grains.
Potassii Chloras .....	0. 250 Gm. = 250 milligrammes.		4 grains.
Potassii Citras .....	1 Gm.		15 grains.

Diuretic.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Potassii Citras Effervescens .....	4 Gm.		60 grains.
Potassii Cyanidum .....	0.010 Gm. = 10 milligrammes.		$\frac{1}{3}$ grain.
Potassii Dichromas .....	0.010 Gm. = 10 milligrammes.		$\frac{1}{3}$ grain.
Potassii et Sodii Tartras .....	8 Gm.		120 grains.
Potassii Ferrocyamidum .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Potassii Hypophosphis .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Potassii Iodidum .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Potassii Nitras .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Potassii Permanganas .....	0.005 Gm. = 65 milligrammes.		1 grain.
Potassii Sulphas .....	2 Gm.		30 grains.
Prunus Virginiana .....	2 Gm.		30 grains.
Pulvis Acetanilidi Compositus .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Pulvis Aromaticus .....	1 Gm.		15 grains.
Pulvis Crete Compositus .....	2 Gm.		30 grains.
Pulvis Effervescens Compositus .....		1 set of two powders.	
Pulvis Glycyrrhizæ Compositus .....	4 Gm.		60 grains.
Pulvis Ipecacuanhæ et Opii .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Pulvis Jalapæ Compositus .....	2 Gm.		30 grains.
Pulvis Morphine Compositus .....	0.500 Gm. = 500 milligrammes.		7½ grains.
Pulvis Rhei Compositus .....	2 Gm.		30 grains.

Pyrethrum.....	2 Gm.	30 grains.
Quassia.....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Quercus.....	1 Gm.	15 grains.
Quinina.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Quininae Bisulphas.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Quininae Hydrobromidum.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Quininae Hydrochloridum.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Quininae Sulfocyanas.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Quininae Sulphas.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Resina.....	0. 250 Gm. = 250 milligrammes.	4 grains.
Resina Jalapæ.....	0. 125 Gm. = 125 milligrammes.	2 grains.
Resina Podophylli.....	0. 015 Gm. = 15 milligrammes.	¼ grain.
	0. 005 Gm. = 5 milligrammes.	$\frac{1}{10}$ grain.
Resina Scammonii.....	0. 200 Gm. = 200 milligrammes.	3 grains.
Resorcinol.....	0. 125 Gm. = 125 milligrammes.	2 grains.
Rhamnus Purshiana.....	1 Gm.	15 grains.
Rheum.....	1 Gm.	15 grains.
Rhus Glabra.....	1 Gm.	15 grains.
Rubus.....	1 Gm.	15 grains.
Sabal.....	1 Gm.	15 grains.
Sabina.....	0. 500 Gm. = 500 milligrammes.	7½ grains.
Safrolum.....	0. 3 Cc.	5 minims.
Salicinum.....	1 Gm.	15 grains.
Salvia.....	2 Gm.	30 grains.
Sanguinaria.....	0. 125 Gm. = 125 milligrammes.	2 grains.
Santoninum.....	0.065 Gm. = 65 milligrammes.	1 grain.

{ Purgative.  
  { Laxative ..

Table of average doses, as given by the U. S. Pharmacopœia, Eighth Decennial Revision—Continued.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metre System.		
Sarsaparilla.....	2 Gm.		30 grains.
Sassafras.....	8 Gm.		120 grains.
Scammonium.....	0.250 Gm. = 250 milligrammes.		4 grains.
Scilla.....	0.125 Gm. = 125 milligrammes.		2 grains.
Scoparius.....	1 Gm.		15 grains.
Scopola.....	0.045 Gm. = 45 milligrammes.		¾ grain.
Scopolamine Hydrobromidum.....	0.0005 Gm. = 0.5 milligramme.		$\frac{1}{128}$ grain.
Scutellaria.....	1 Gm.		15 grains.
Senega.....	1 Gm.		15 grains.
Sennu.....	4 Gm.		60 grains.
Serpentaria.....	1 Gm.		15 grains.
Serum Antidiphthericum.....			3,000 units.
			500 units.
Simipis Alba.....	8 Gm.		120 grains.
Simipis Nigra.....	8 Gm.		120 grains.
Sodii Acetas.....	1 Gm.		15 grains.
Sodii Arsenas.....	0.005 Gm. = 5 milligrammes.		$\frac{1}{20}$ grain.
Sodii Arsenas Fissicatus.....	0.003 Gm. = 3 milligrammes.		$\frac{1}{20}$ grain.
Sodii Benzons.....	1 Gm.		15 grains.
Sodii Bicarbonas.....	1 Gm.		15 grains.



Sodii Bisulphis.....	0.500 Gm. = 500 milligrammes.	7½ grains.
Sodii Boras .....	0.500 Gm. = 500 milligrammes.	7½ grains.
Sodii Bromidum .....	1 Gm.	15 grains.
Sodii Carbonas Monohydratus .....	0.250 Gm. = 250 milligrammes.	4 grains.
Sodii Chloras .....	0.250 Gm. = 250 milligrammes.	4 grains.
Sodii Chloridum .....	16 Gm.	240 grains.
Sodii Citras .....	1 Gm.	15 grains.
Sodii Hypophosphis .....	1 Gm.	15 grains.
Sodii Iodidum .....	0.500 Gm. = 500 milligrammes.	7½ grains.
Sodii Nitras .....	1 Gm.	15 grains.
Sodii Nitris .....	0.065 Gm. = 65 milligrammes.	1 grain.
Sodii Phenolsulphonas .....	0.250 Gm. = 250 milligrammes.	4 grains.
Sodii Phosphas .....	2 Gm.	30 grains.
Sodii Phosphas Effervescens .....	8 Gm.	120 grains.
Sodii Phosphas Exsiccatus .....	1 Gm.	15 grains.
Sodii Pyrophosphas .....	2 Gm.	30 grains.
Sodii Salicylas .....	1 Gm.	15 grains.
Sodii Sulphas .....	16 Gm.	240 grains.
Sodii Sulphis .....	1 Gm.	15 grains.
Sodii Thiosulphas .....	1 Gm.	15 grains.
Sparteinae Sulphas.....	0.010 Gm. = 10 milligrammes.	½ grain.
Spigelia .....	4 Gm.	60 grains.
Spiritus Etheris .....	4 Cc.	1 fluidrachm.
Spiritus Etheris Compositus .....	4 Cc.	1 fluidrachm.
Spiritus Etheris Nitrosi .....	2 Cc.	30 minims.
Spiritus Ammoniae .....	1 Cc.	15 minims.

Table of average doses, as given by the U. S. Pharmacopœia, Eighth Decennial Revision—Continued.

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Spiritus Ammonie Aromaticus.....	2 Cc.	30 minims.
Spiritus Amygdalæ Amare .....	0.5 Cc.	8 minims.
Spiritus Anisi.....	4 Cc.	1 fluidrachm.
Spiritus Camphoræ.....	1 Cc.	15 minims.
Spiritus Chloroformi .....	2 Cc.	30 minims.
Spiritus Cinnamomi .....	2 Cc.	30 minims.
Spiritus Gaultheriæ.....	2 Cc.	30 minims.
Spiritus Glycerylis Nitratis.....	0.05 Cc.	1 minim.
Spiritus Juniperi .....	2 Cc.	30 minims.
Spiritus Juniperi Compositus.....	8 Cc.	2 fluidrachms.
Spiritus Lavandulæ .....	2 Cc.	30 minims.
Spiritus Menthæ Piperitæ.....	2 Cc.	30 minims.
Spiritus Menthæ Viridis .....	2 Cc.	30 minims.
Staphisagria .....	0.065 Gm. = 65 milligrammes.	1 grain.
Stillingia.....	2 Gm.	30 grains.
Stramonium .....	0.065 Gm. = 65 milligrammes.	1 grain.
Strontii Bromidum .....	1 Gm.	15 grains.
Strontii Iodidum.....	0.500 Gm. = 500 milligrammes.	7½ grains.
Strontii Salicylas.....	1 Gm.	15 grains.
Strophanthinum .....	0.0003 Gm. = 0.3 milligramme.	$\frac{1}{200}$ grain.

Strophanthus .....	0.065 Gm. = 65 milligrammes.	1 grain.
Strychnina .....	0.001 Gm. = 1 milligramme.	$\frac{1}{84}$ grain.
Strychninae Nitræs .....	0.001 Gm. = 1 milligramme.	$\frac{1}{84}$ grain.
Strychninae Sulphas .....	0.001 Gm. = 1 milligramme.	$\frac{1}{84}$ grain.
Styrax .....	1 Gm.	15 grains.
Sulphonethylmethanum .....	1 Gm.	15 grains.
Sulphonmethanum .....	1 Gm.	15 grains.
Sulphur Lotum .....	4 Gm.	60 grains.
Sulphur Precipitatum .....	4 Gm.	60 grains.
Sulphur Sublimatum .....	4 Gm.	60 grains.
Sumbul .....	2 Gm.	30 grains.
Syrupus Acidi Hydriodici .....	4 Cc.	1 fluidrachm.
Syrupus Amygdalæ .....	4 Cc.	1 fluidrachm.
Syrupus Calcii Lactophosphatis .....	8 Cc.	2 fluidrachms.
Syrupus Calcis .....	2 Cc.	30 minims.
Syrupus Ferri Iodidi .....	1 Cc.	15 minims.
Syrupus Ferri, Quininae et Strychninae Phosphatum .....	4 Cc.	1 fluidrachm.
Syrupus Hypophosphitum .....	8 Cc.	2 fluidrachms.
Syrupus Hypophosphitum Compositus .....	8 Cc.	2 fluidrachms.
Syrupus Ipecacuanhæ .....	1 Cc.	15 minims.
Syrupus Krameriaæ .....	15 Cc.	4 fluidrachms.
Syrupus Lactucari .....	4 Cc.	1 fluidrachm.
Syrupus Pleis Liquidæ .....	8 Cc.	2 fluidrachms.
Syrupus Pruni Virginianæ .....	4 Cc.	1 fluidrachm.
Syrupus Rhei .....	8 Cc.	2 fluidrachms.

{ Expectorant.  
} Emetic.

Table of average doses, as given by the U. S. Pharmacopœia, Eighth Decennial Revision—Continued.

PREPARATION.	AVERAGE DOSE.		Approximate Equivalent Ordinary System.
	Metric System.		
Syrupus Rhei Aromaticus.....	8 Cc.		2 fluidrachms.
Syrupus Rubi.....	4 Cc.		1 fluidrachm.
Syrupus Sarsaparillæ Compositus.....	16 Cc.		4 fluidrachms.
Syrupus Scillæ.....	2 Cc.		30 minims.
Syrupus Scillæ Compositus.....	2 Cc.		30 minims.
Syrupus Senegæ.....	4 Cc.		1 fluidrachm.
Syrupus Sennæ.....	4 Cc.		1 fluidrachm.
Syrupus Tolutani.....	16 Cc.		4 fluidrachms.
Syrupus Zingiberis.....	16 Cc.		4 fluidrachms.
Tamarindus.....	16 Gm.		240 grains.
Taraxacum.....	8 Gm.		120 grains.
Terebinth.....	0.5 Cc.		8 minims.
Terpini Hydras.....	0.125 Gm. = 125 milligrammes.		2 grains.
Thymol.....	0.125 Gm. = 125 milligrammes.		2 grains.
Tinctura Aconiti.....	0.6 Cc.		10 minims.
Tinctura Aloës.....	2 Cc.		30 minims.
Tinctura Aloës et Myrrhæ.....	2 Cc.		30 minims.
Tinctura Arnice.....	1 Cc.		15 minims.
Tinctura Asafœtidæ.....	1 Cc.		15 minims.
Tinctura Aurantii Amari.....	4 Cc.		1 fluidrachm.



Tinctura Aurantii Dulcis.....	4 Cc.	1 fluidrachm.
Tinctura Belladonnae Foliorum.....	0.5 Cc.	8 minims.
Tinctura Benzoini.....	1 Cc.	15 minims.
Tinctura Benzoini Composita.....	2 Cc.	30 minims.
Tinctura Calumbe.....	4 Cc.	1 fluidrachm.
Tinctura Cannabis Indicæ.....	0.6 Cc.	10 minims.
Tinctura Cantharidis.....	0.3 Cc.	5 minims.
Tinctura Capsici.....	0.5 Cc.	8 minims.
Tinctura Cardamomi.....	4 Cc.	1 fluidrachm.
Tinctura Cardamomi Composita.....	4 Cc.	1 fluidrachm.
Tinctura Cimicifugæ.....	4 Cc.	1 fluidrachm.
Tinctura Cinchonæ.....	4 Cc.	1 fluidrachm.
Tinctura Cinchonæ Composita.....	4 Cc.	1 fluidrachm.
Tinctura Cinnamomi.....	2 Cc.	30 minims.
Tinctura Colchici Seminis.....	2 Cc.	30 minims.
Tinctura Digitalis.....	1 Cc.	15 minims.
Tinctura Ferri Chloridi.....	0.5 Cc.	8 minims.
Tinctura Gallæ.....	4 Cc.	1 fluidrachm.
Tinctura Gambir Composita.....	4 Cc.	1 fluidrachm.
Tinctura Gelsemii.....	0.5 Cc.	8 minims.
Tinctura Gentianæ Composita.....	4 Cc.	1 fluidrachm.
Tinctura Guaiaci.....	4 Cc.	1 fluidrachm.
Tinctura Guaiaci Ammoniata.....	2 Cc.	30 minims.
Tinctura Hydrastis.....	4 Cc.	1 fluidrachm.
Tinctura Hyoscyami.....	1 Cc.	15 minims.
Tinctura Iodi.....	0.1 Cc.	1½ minims.

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Tinctura Ipecacuanhæ et Opii.....	0.5 Cc.	8 minims.
Tinctura Kino.....	4 Cc.	1 fluidrachm.
Tinctura Kramerie.....	4 Cc.	1 fluidrachm.
Tinctura Lactucarii.....	2 Cc.	30 minims.
Tinctura Lavandule Composita.....	2 Cc.	30 minims.
Tinctura Lobellie.....	1 Cc.	15 minims.
	4 Cc.	1 fluidrachm.
Tinctura Moschi.....	4 Cc.	1 fluidrachm.
Tinctura Myrrhæ.....	1 Cc.	15 minims.
Tinctura Nucis Vomice.....	0.6 Cc.	10 minims.
Tinctura Opii.....	0.5 Cc.	8 minims.
Tinctura Opii Camphorata.....	8 Cc.	2 fluidrachms.
Tinctura Opii Deodorati.....	0.5 Cc.	8 minims.
Tinctura Physostigmatis.....	1 Cc.	15 minims.
Tinctura Quassie.....	2 Cc.	30 minims.
Tinctura Rhei.....	4 Cc.	1 fluidrachm.
Tinctura Rhei Aromatica.....	2 Cc.	30 minims.
Tinctura Sanguinariæ.....	1 Cc.	15 minims.
Tinctura Scillæ.....	1 Cc.	15 minims.
Tinctura Serpentariæ.....	4 Cc.	1 fluidrachm.

} Expectorant.  
} Emetic.

Tinctura Stramonii.....	0.5 Cc.	8 minims.
Tinctura Strophanthi.....	0.5 Cc.	8 minims.
Tinctura Tolutana.....	2 Cc.	30 minims.
Tinctura Valerianæ.....	4 Cc.	1 fluidrachm.
Tinctura Valerianæ Ammoniata.....	2 Cc.	30 minims.
Tinctura Veratri.....	1 Cc.	15 minims.
Tinctura Zingiberis.....	2 Cc.	30 minims.
Triticum.....	8 Gm.	120 grains.
Trituratio Elaterini.....	0.030 Gm. = 30 milligrammes.	$\frac{1}{2}$ grain.
Uva Ursi.....	2 Gm.	30 grains.
Valeriana.....	2 Gm.	30 grains.
Vanilla.....	1 Gm.	15 grains.
Vanillinum.....	0.030 Gm. = 30 milligrammes.	$\frac{1}{2}$ grain.
Veratrina.....	0.002 Gm. = 2 milligrammes.	$\frac{1}{30}$ grain.
Veratrum.....	0.125 Gm. = 125 milligrammes.	2 grains.
Viburnum Opulus.....	2 Gm.	30 grains.
Viburnum Prunifolium.....	2 Gm.	30 grains.
Vinum Antimonii.....	1 Cc.	15 minims.
Vinum Cocce.....	16 Cc.	4 fluidrachms.
Vinum Colchici Seminibus.....	2 Cc.	30 minims.
Vinum Ergotæ.....	8 Cc.	2 fluidrachms.
Vinum Ferri.....	8 Cc.	2 fluidrachms.
Vinum Ferri Amarum.....	8 Cc.	2 fluidrachms.
Vinum Ipecacuanhæ.....	1 Cc.	15 minims.
Vinum Opii.....	0.5 Cc.	8 minims.
Xanthoxylum.....	2 Gm.	30 grains.

Table of average doses, as given by the U. S. Pharmacopœia, eighth decennial revision—Continued.

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Zinci Acetas .....	0. 125 Gm. = 125 milligrammes.	2 grains.
Zinci Bromidum .....	0. 125 Gm. = 125 milligrammes.	2 grains.
Zinci Iodidum .....	0. 065 Gm. = 65 milligrammes.	1 grain.
Zinci Oxidum .....	0. 250 Gm. = 250 milligrammes.	4 grains.
Zinci Phenolsulphonas .....	0. 125 Gm. = 125 milligrammes.	2 grains.
Zinci Sulphas .....	1 Gm.	15 grains.
Zinci Valeras .....	0. 125 Gm. = 125 milligrammes.	2 grains.
Zingiber .....	1 Gm.	15 grains.
	.....Emetic.	



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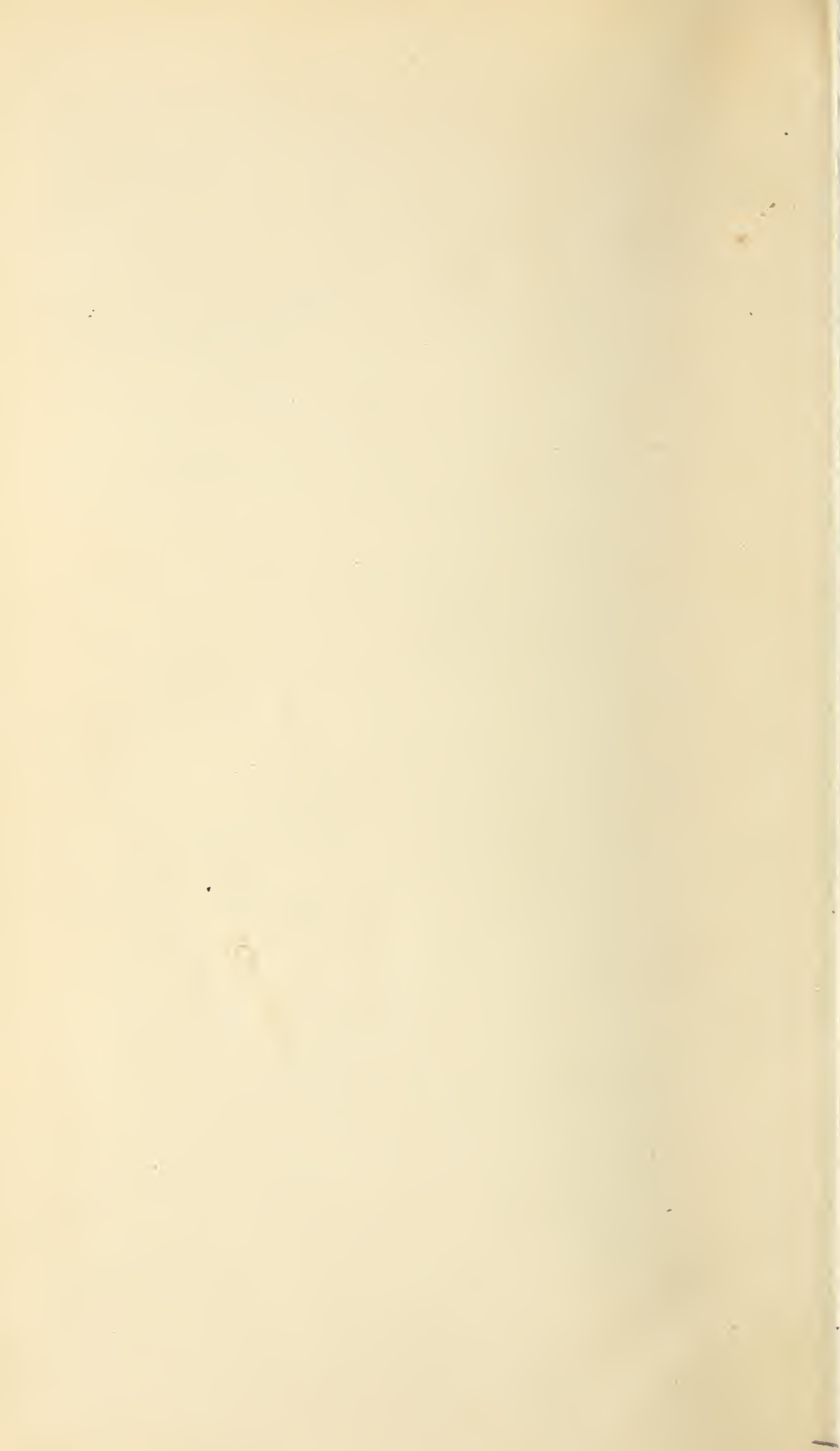
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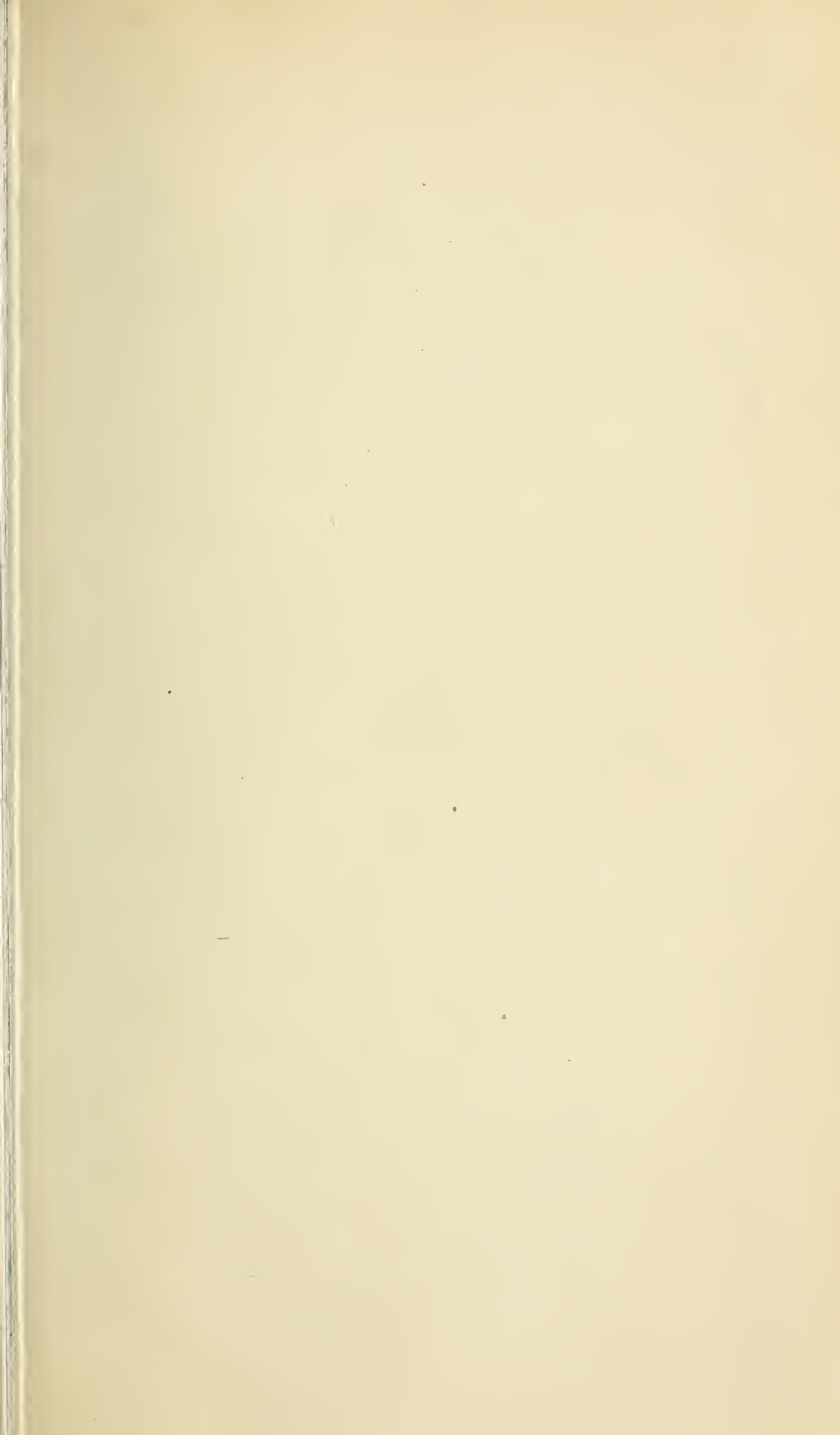
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