THE ACTION OF DIPHTHERIA AND DIPHTHERIA-LIKE BACILLI ON VARIOUS SUGARS AND CARBO-HYDRATES.

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During the last few years a considerable number of bacilli have been described by various observers, which more or less resemble diphtheria bacilli in morphology and in some cultural characters. These bacilli have been obtained not only from the human mouth, nose, and eye, but also from the ear, skin, and genital organs. Organisms almost indistinguishable from diphtheria bacilli have also been discovered in the brain and internal viscera. Moreover similar bacilli have been isolated from various animals, both healthy and diseased, and from milk. Some of these bacilli are totally non-virulent to laboratory animals and to man, while others are virulent both for man and for animals.

Bacilli identical with the diphtheria bacillus in all respects except virulence, commonly known as non-virulent diphtheria bacilli, are occasionally found in the human mouth and nose. Hofmann's pseudo-diphtheria bacillus is a common inhabitant of the healthy throat and nose, and the xerosis bacillus is frequently present in the normal eye. Apart from these organisms non-virulent diphtheria-like bacilli, differing from the diphtheria bacillus in some more or less important cultural characters, have been isolated from the human mouth by Gordon (1901), Graham-Smith (1904), and Hamilton (1904); and bacilli virulent for laboratory animals by Williams (1898), De Simoni (1898), Davis (1899), Ruediger (1903), Hamilton (1904), and Hamilton and Horton (1906).

Non-virulent diphtheroid bacilli have been isolated from the nose by Cautley (1894), De Simoni (1898), and Gordon (1901), from the eye by Griffith (1901), and Gordon (1901), from the ear by Davis (1898), De Simoni (1899), Marzinowsky (1900), Warnecke (1900), Gordon (1901),

Forbes (1903), Graham-Smith (1904), and Hamilton (1904), and virulent bacilli by Hamilton (1904). Diphtheria-like bacilli have been found in the lesions of vaccinia and variola by Neisser (1888), Besser (1893), De Simoni (1899), Klein (1897), Nakanishi (1900), Brown (1903), Sanfelice and Malato (1903), and Galli-Valero (1904), in the lesions of leprosy by Babes (1899), Spronck (1898), Levy (1897), Czapelewski (1898), Barranikow (1899), Teich (1899), and Kedrowski (1901), and in eczema and other skin lesions by Neisser (1888), Peters (1897), Paffenholz (1895), Bergey (1898), Warnecke (1900), and Cobbett (IV, 1901). Similar organisms have been isolated from the female genital organs by Bergey (1898), Foulerton and Bonney (1903), and Robertson and McRae (V, 1905), and from the male urethra by Pfeiffer (1903), Foulerton and Bonney (1903), and Robertson and McRae (V, 1905), and from the urine by Bergey (1898).

Kruse and Pasquale (1894) found diphtheroid bacilli in the pus of a liver abscess, Robertson, McRae and Jeffery (V, 1903) in the bronchi, lung tissue, stomach, brain, bone marrow, and inflamed portions of the ileum in general paralytics, Johnston and Goodall (1902) in the blood and brain of a patient dying of mania, and Howard (1894) on the heart valves of a patient dying of ulcerative endocarditis.

Diphtheroid bacilli indistinguishable from diphtheria bacilli in morphology have been isolated from milk by McClure (1898), Eyre (1900), Klein (1901), and Bergey (1904). Diphtheria-like bacilli have also been obtained from animals by the following observers; from lesions of the lungs of rats by Klein (1903), from the cutaneous lesions in a leprosy-like disease of rats by Dean (1905), from abscesses in laboratory mice by Bergey (1904), and from the eyes of normal guinea-pigs and dogs by Graham-Smith (1904). They have also been obtained from the mouths of diseased and normal birds by Macfadyen and Hewlett (1900), Harrison (1901), Guerin (1901), and Graham-Smith (1904), and from calf lymph by Levy and Fickler (1900).

Many of the bacilli described by the investigators mentioned so closely resemble the diphtheria bacillus in morphology, including a positive reaction to Neisser's stain, that differentiation by means of microscopic preparations is impossible. In many cases, moreover, several of the cultural characteristics are identical with those of the diphtheria bacillus.

In spite of these observations an examination of even the recent writings on the bacteriology of diphtheria shows that many workers are still content to found far-reaching conclusions on the morphology in

culture alone. Some have not even gone so far, but have based their statements on the direct examination of smears. In fact from not a few of these papers it is evident that the writers are scarcely aware that the identification of bacteria depends on anything else than their morphological characters, and such important aids to classification as their action on sugars and the effects of animal inoculations are often not even mentioned. Conclusions based on such evidence can have little value in the eyes of bacteriologists, but are apt to mislead those who have no practical acquaintance with the subject.

In view of the rapidly accumulating evidence that diphtheroid bacilli are not uncommon, it becomes necessary to isolate and test as far as possible all organisms resembling diphtheria bacilli, which are met with outside the human throat and nose. Even in the latter situations it is most desirable to thoroughly investigate such bacilli, including their action on animals, before venturing on any conclusions as to the occurrence of virulent diphtheria bacilli in persons not recently exposed to the disease.

Most observers have confined their experiments to observing the morphological and cultural characters of the bacilli on the ordinary media, their reaction in media to which glucose has been added, and their action on guinea-pigs. A few have further endeavoured to ascertain whether diphtheria bacilli can be differentiated from organisms resembling them by their action on media containing various sugars and carbo-hydrates. These tests appear to afford a means of further differentiating the bacilli belonging to the diphtheria group.

The present paper contains some recent experiments by the writer on this subject and a summary of some of the experiments recorded by recent investigators.

Diphtheria bacilli. L. Martin (1898) working with ·5 % solutions in broth found that diphtheria bacilli produced acid from glucose, laevulose, saccharose, glycerine, and galactose, but not from glycogen, lactose, maltose, raffinose, arabinose, dulcite, or mannite. The careful experiments of Theobald Smith (1896), however, show that neither lactose, nor saccharose are acted on, and most other writers who have mentioned the subject agree that acid is not produced from saccharose. Blumenthal (1897) disagrees with both these writers in stating that lactose is split up by the diphtheria bacillus. More recently Knapp (1904) working with the serum water medium of Hiss has investigated the acid-forming power of 27 races of diphtheria bacilli. He finds that when glucose,

maltose, dextrin, or mannite are present the medium is coagulated and made acid, but that lactose and saccharose are not acted on. Hamilton and Horton (1906) found that all races of typical diphtheria bacilli produce acid in media to which dextrine has been added.

All workers agree that diphtheria bacilli act rapidly and powerfully on glucose and produce acid, but the accounts of its action on the other substances are not in agreement. Lack of uniformity in method probably accounts for this fact.

It is well known that recently isolated diphtheria bacilli show great differences in their capacity for growing in broth. Some grow luxuriantly, while others produce a very scanty growth. The latter, however, after several generations in broth, when they have become accustomed to the medium, grow as well as the former. Those races which grow poorly can scarcely be expected to split up substances in solution as rapidly as those which grow well, especially those substances on which this organism acts feebly even under the most favourable conditions.

Certain experiments on virulence illustrate the great differences in results which may arise from the unequal growths of various races of diphtheria bacilli in broth. Williams (1902) found that, when first isolated, broth cultures of some races of diphtheria bacilli showed extremely scanty growth. "Such broth cultures gave very little reaction in guinea-pigs except in large amounts, although the bacilli themselves when inoculated from serum cultures were decidedly virulent. In ascites broth, however, where they grew rapidly and abundantly they showed a high degree of toxicity. After ascites broth was used to test toxicity, all the specifically virulent diphtheria bacilli,—about one hundred cultures—segmented and non-segmented varieties, were found to be highly toxic for guinea-pigs. The largest dose of a two to six day culture in ascites broth which was required to produce death in this animal was one-fiftieth cubic centimetre, the average being, one one-hundredth cubic centimetre."

In testing the acid-forming power, therefore, the bacilli should be grown in broth until they have become accustomed to the medium, and grow well in it, or a medium should be used in which the majority of races grow well. Broth to which ascites fluid or serum has been added or the serum-water medium of Hiss fulfil this condition[1]. Incubation should be extended over several days so that a late action should not be overlooked.

[1] Serum...1 part. Water...3 parts. Add 1 % of the substance to be tested and sterilise on three consecutive days in steam at 100° C.

Hofmann's pseudo-diphtheria bacillus. All workers agree that this organism does not produce acid in the presence of any of these substances, although abundant growth occurs.

Xerosis bacillus. While most writers[1] state that the xerosis bacillus forms no acid in ordinary broth or in media to which glucose has been added, Knapp (1904) found that this organism produced acid with glucose, maltose, mannite, and saccharose, but not with dextrine.

Griffith (1901) could find no acid production with lactose, and Benham (1906) says that acid is not formed in the presence of lactose, saccharose, or maltose.

Bacillus coryzae segmentosus. Benham (1906) finds that after seven days' growth this organism generally produces acid with glucose, lactose, saccharose, and maltose, and Gordon (1901) states that it produces a feeble acid reaction with glucose.

Other diphtheria-like bacilli. Numerous other diphtheria-like bacilli have been isolated from various sources which are capable of producing acid with glucose. In most cases their reaction on other substances has not been tested.

In the experiments described in this paper 23 races of diphtheria bacilli, 20 races of Hofmann's bacilli, 3 races of the xerosis bacillus, 2 races of *B. coryzae segmentosus*, and 7 races of other diphtheria-like bacilli were tested, for their action on 1 % of glucose, galactose, laevulose, maltose, dextrine, glycerine, lactose, mannite, and saccharose in the serum medium of Hiss. In this medium two series of experiments were made, in the first the organisms were grown for 3 days at 37° C., and in the second for 10 days. After 24—48 hours' incubation the degree of growth was noted and the condition of the medium, and in those cases in which the growth was poor a second culture was made. The accompanying table shows the results after 10 days' incubation. With the formation of much acid the medium becomes opaque and is firmly clotted. When less acid is formed the medium may only be partially clotted or have a gelatinous consistency. In some cases, however, a small amount of acid may be produced without any change occurring in the appearance of the medium. Several races were also tested in very slightly alkaline broth, free from muscle sugar, to which 1 % of the substances mentioned above had been added. In this case growth was only continued for 48 hours. Litmus was used as the indicator.

[1] Benham (1906), Gordon (1901), Griffith (1901), Lawson (1899), Axenfeld (1898), Franke (1898), Eyre (1897).

Diphtheria bacilli. Of the diphtheria bacilli tested 18 races were fully virulent to guinea-pigs and 5 were non-virulent. 7 were derived from clinical cases of diphtheria at the beginning of the disease, 5 from convalescents between the 10th and 56th day after the disappearance of the symptoms, 10 from healthy children infected with diphtheria bacilli by contact, and 1 from a case clinically diagnosed as "sore-throat."

An acid reaction was invariably produced in media containing glucose, galactose, and laevulose. In Hiss' medium (10 day cultures) every specimen produced acid with maltose, all but one with glycerine, and all but two with dextrine. With lactose 6 showed a marked reaction, 10 a slight acid reaction, and 4 no acid reaction, while in 3 the reaction was doubtful. Marked coagulation of the medium occurred in almost every tube containing glucose, galactose, maltose, and dextrine, and in half the tubes containing glycerine and lactose. In the latter media many of the tubes were only partially coagulated, and in some the medium was only made more viscid or gelatinous. No acid reaction or other change was ever produced with mannite or saccharose. In tubes incubated for three days the acid reaction failed to appear in many of the tubes containing lactose and glycerine, and in some containing dextrine and maltose. In broth cultures acid was always produced with glucose, galactose, and dextrine, and sometimes with lactose, maltose, and glycerine.

Hofmann's bacillus. Experiments were made with 20 races of Hofmann's bacillus, but in no case was any acid production noted in the presence of any of these substances. Three of these races were derived from clinical cases of diphtheria, four from convalescents, four from contacts infected with diphtheria bacilli, three from persons suffering from sore-throat, and the rest from normal throats and noses.

If the contention that Hofmann's bacilli are merely attenuated diphtheria bacilli be true, it would seem probable that some of these organisms when isolated from the throats of clinical cases of diphtheria or convalescents would still be capable of producing acid, at any rate from glucose. The fact that this does not occur is in favour of the view that these organisms belong to distinct species.

The xerosis bacillus. Three races of the xerosis bacillus derived from normal eyes were tested. Acid production was not observed in broth after 48 hours' growth, and only occurred in the medium of Hiss after several days' incubation. A small amount of acid was produced

with glucose, laevulose, and glycerine, and a still smaller amount with saccharose.

B. coryzae segmentosus. Two races of this organism derived from the noses of persons suffering from nasal catarrh were tested. Acid was produced with glucose, galactose, and laevulose, but not with the other substances.

Other diphtheria-like bacilli. Three races of diphtheria-like bacilli derived from normal ears were tested, but produced no acid.

A diphtheria-like bacillus from an urethral discharge, another from an ulcer of the mouth, and a third from the mouth forming a hard scaly growth on serum, produced acid in the media containing glucose, galactose, laevulose, and maltose. In some of these cases the quantity produced was so slight that no coagulation took place in the medium of Hiss. A diphtheria-like bacillus derived from a fowl produced acid in small quantities from glucose, galactose, and maltose, and a doubtful reaction with mannite.

Summary.

The experiments here recorded are not sufficiently numerous to justify any decided opinions as to the value of the tests with these various substances in differentiating certain bacilli which very closely resemble the diphtheria bacillus. They show, however, that most of the diphtheria-like organisms tested produce less acid than the diphtheria bacillus. Hofmann's bacillus and a diphtheria-like bacillus from the normal ear can be easily differentiated, since they form no acid. Any bacillus which acts on mannite or saccharose could also be easily differentiated.

Table showing the reaction of diphtheria bacilli from different sources on various sugars and carbo-hydrates in the serum-water medium of Hiss and in broth.

	Source	Virulence	Hiss' medium (10 days' growth)									Broth (48 hours' growth)							
			Glucose	Galactose	Lævulose	Maltose	Dextrine	Glycerine	Lactose	Mannite	Saccharose	Glucose	Galactose	Maltose	Dextrine	Glycerine	Lactose	Mannite	Saccharose
1.	Clinical case	virulent	C	C	C	C	C	C	C	–	–	+							
			+	+	+	+	+	+	+	0	0								
2.	Convalescent (26th day)	,,	C	C	·	C	C	c	C	–	–	+	+	0		0	0	0	0
			+	+	·	+	+	+	+	0	0								
3.	,, (10th day)	,,	C	C	C	C	C	C	c	–	–	+							
			+	+	+	+	+	+	*	0	0								
4.	Contact	,,	C	C	C	C	C	C	C	–	–	+							
			+	+	+	+	+	+	*	0	0								
5.	,,	,,	C	C	C	C	C	C	C	–	–	+							
			+	+	+	+	+	+	*	0	0								
6.	,,	non-virulent	C	C	C	C	C	C	c	–	–	+							
			+	+	+	+	+	+	*	0	0								
7.	Clinical case	virulent	C	C	C	C	C	c	C	–	–	+	+	0	+	0	0	0	0
			+	+	+	+	+	*	+	0	0								
8.	,, ,,	,,	C	C	C	C	C	c	C	–	–	+	+	0	+	0	0	0	0
			+	+	+	+	+	*	+	0	0								
9.	,, ,,	,,	C	C	C	C	C	c	C	–	–	+	+	+	+	0	*	0	0
			+	+	+	+	+	*	+	0	0								
10.	Contact	non-virulent	C	C	C	C	c	C	c	–	–	+							
			+	+	+	+	+	+	*	0	0								
11.	Convalescent (56th day)	virulent	C	C	C	C	c	C	c	–	–	+							
			+	+	+	+	*	+	*	0	0								
12.	Contact	,,	C	C	·	C	C	c	c	–	–	+	+	*	+	0	0	0	0
			+	+	·	+	+	*	*	0	0								
13.	Clinical case	,,	C	C	C	c	c	C	C	–	–	+	+	*	*	*	0	0	0
			+	+	+	+	*	+	*	0	0								
14.	Contact	,,	C	C	C	C	C	c	c	–	–	+	+	+	*	0	0	0	0
			+	+	+	+	+	*	*	0	0								
15.	Clinical case	,,	C	C	·	C	C	–	C	–	–	+							
			+	+	·	+	+	*	+	0	0								
16.	Contact	non-virulent	C	C	·	C	C	–	–	–	–	+	+	0	+	*	*	0	0
			+	+	·	+	+	*	0	0	0								
17.	,,	,,	C	C	·	C	C	c	–	–	–	+	+	*	+	0	0	0	0
			+	+	·	+	+	*	*	0	0								
18.	Convalescent (35th day)	virulent	C	C	C	c	c	C	g	–	–	+	+	0	+	0	0	0	0
			+	+	+	+	*	+	n	0	0								
19.	Contact	,,	C	C	C	C	c	C	g	–	–	+	*	0	*	0	0	0	0
			+	+	+	+	n	+	n	0	0								
20.	Convalescent (46th day)	,,	C	C	C	C	c	C	–	–	–	+							
			+	+	+	+	+	+	n	0	0								
21.	Clinical case	,,	C	C	C	c	C	c	–	–	–	+							
			+	+	+	+	*	*	0	0	0								
22.	Contact	,,	C	C	C	C	C	C	–	–	–	+							
			+	+	+	+	*	*	0	0	0								
23.	"Sore-throat" ("Sheath form")	non-virulent	C	g	C	C	–	–	–	–	–	+							
			+	*	+	+	0	0	0	0	0								

C = complete coagulation.
c = partial coagulation.
g = medium rendered of a gelatinous consistency.
– = no change in appearance.
+ = markedly acid.
* = acid.
n = neutral reaction.
0 = no acid formation.
· = not tested.

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Table showing the reaction of diphtheria-like bacilli from different sources on various sugars and carbo-hydrates in the serum-water medium of Hiss and in broth.

Bacillus	Hiss' medium: Glucose	Galactose	Laevulose	Maltose	Dextrine	Glycerine	Lactose	Mannite	Saccharose	Broth: Glucose	Galactose	Maltose	Dextrine	Glycerine	Lactose	Mannite	Saccharose
Hofmann's bacillus																	
3 races from diphtheria cases	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4 ,, ,, convalescents ...	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4 ,, ,, contacts ...	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3 ,, ,, "sore-throats"	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6 ,, ,, normal throats	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Xerosis bacillus. 3 races ...	C	–	C	–	–	C	–	–	–	*?							
	+	0	+	0	0	*	0	0	*?								
B. coryzae segmentosus. 2 races	C	c	C	–	–	–	–	–	–	*							
	+	*	+	0	0	0	0	0	0								
Other diphtheria-like bacilli																	
from normal ears. 3 races...	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
from urethra	–	–	–	–	–	–	–	–	–	*	0	0	0	0	0	0	0
	*	*	*	*	0	0	0	0	0								
from ulcer of mouth... ...	–	–	–	–	–	–	–	–	–	+							
	*	*	*	*	0	0	0	0	0								
from the throat	C	C	C	–	–	–	–	–	–	+							
	+	+	+	*	0	0	0	0	0								
from a fowl	–	–	•	–	–	–	–	–	–	0	0	0	0	0	0	0	0
	*	*	•	*	0	0	0	0	0								

All these organisms are non-virulent to guinea-pigs.

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