

with a profuse urticarial eruption. The same thing happened within half an hour of its first inoculation with pure diphtheria toxin. After its second dose of toxin in addition to the urticaria it was thrown into a profuse perspiration. I thereupon shaved an area of skin upon its flanks of about eight inches in diameter and collected some of the moisture in one of the bulbed tubes before described. This was injected into a guinea-pig and gave rise to a marked and typical local reaction.

*Tetanus.*—I have obtained sweat from one patient with acute traumatic tetanus, but though a considerable quantity was injected I obtained no positive effects.

*Conclusions.*—The above experimental evidence seems to me to have a practical bearing upon therapeutics inasmuch as it furnishes a rational basis for the old empirical method of treatment—viz., that of "sweating a fever." The artificial encouragement of the sweating no doubt assists in the elimination of the toxin by way of the skin leaving less behind to poison the tissues. I hope in a further communication to detail the results of the experimental examination of the sweat of patients with acute rheumatism, which I hope will assist in throwing some light upon the nature of the rheumatic toxin.

Sudbury, Middlesex.

## ON THE SERUM DIAGNOSIS OF TYPHOID FEVER, WITH ESPECIAL REFERENCE TO THE BACILLUS OF GÄRTNER AND ITS ALLIES

By HERBERT E. DURHAM, M.A., M.B. CAMB.,  
F.R.C.S. ENG.,

GROCCERS' RESEARCH SCHOLAR.

(From the Pathological Laboratory of the University of Cambridge.)

ELSEWHERE I have called attention to the possible importance in the serum diagnosis of typhoid fever of Landsteiner's observation made in Professor Gruber's Institute that Gärtner's bacillus reacts positively with typhoid serum. That the same occurred in the case of the serum of typhoid fever patients I demonstrated at Liverpool in February, 1897.<sup>1</sup> It seemed that further investigation should be made upon this point, and the recent epidemics at Maidstone, Clifton, and King's Lynn have afforded an opportunity for inquiry. I must here express my sincere thanks to Mr. P. Adams and Dr. Poole, of Maidstone, Dr. Lansdown, of Clifton, and Dr. Plowright and Dr. Sumpter, of Lynn, for most kindly giving me facilities for obtaining serum and also for sending me many samples at their own personal inconvenience.

Before entering into the question of the serum reactions it will be well to make a few preliminary remarks upon the bacillus enteritidis (Gärtner), an organism which has hardly received the attention that it deserves in this country and which must not be confounded with the unhappily named bacillus enteritidis sporogenes of Dr. Klein. Authors have been in the habit of grouping the typhoid and colon bacilli in rather a promiscuous way—the "typhoid-like" of one observer being a "colon-like" to another.

The whole class may be divided into three groups:—(1) the Eberth group includes the typhoid bacillus and its near allies (these are almost unknown); (2) the Gärtner group includes bacillus enteritidis and its near allies (these have not yet been sufficiently worked out); and (3) the Escherich group includes the true bacillus coli and its near allies (these also have not yet been sufficiently worked out). I do not propose to enter here into the discussion of further groups of bacilli which in some respects resemble those of Group 3, though widely differing from those of Groups 1 and 2.

In the literature of the subject it appears probable that members of the Gärtner group have been confounded with those of Group 1 and 2. However, they are not very difficult to distinguish in practice. In Germany, Holland, and Belgium, a number of outbreaks of "meat poisoning" have been carefully investigated; in many of these the

causation of illness has been ascribed to certain bacilli or their toxic products, which bears a striking family resemblance to the original account of Gärtner; the individual differences which have been noticed are apparently comparatively of little importance. These bacilli have been isolated from the infected meat (often in the form of "German sausage"), vomit, and faeces, as also from the organs in fatal cases. A perusal of Dr. Günther's paper will show what care and patience may be required in working out a case of "meat poisoning" with success.

In the accompanying table in which the three groups are contrasted the description refers to characters which are presented by the actual bacillus of Gärtner at my disposal; so far as Gärtner's description goes, it is at variance only in the number of flagella (from four to eight) and the production of gas bubbles in lactose media. At the time when he wrote the technique of cilia staining was not so perfect as at present.<sup>2</sup> Other writers as well as Gärtner have given their bacilli credit of producing gas, though small in amount, in lactose media. As they did not use media free of muscle sugar ("bouillon") their statements are without value. The terms "paratyphoid" and "paracoli," about the relative merits of which there has been some discussion between Widal and Achard, do not appear to me to be at all appropriate; the group is evidently quite distinct from both typhoid and coli. Moreover, there are "Escherich-like" bacilli which are also unable to "ferment" lactose.

It will be observed that the bacillus Gärtner only differs from the bacillus Eberth in being able to produce gas bubbles in the presence of glucose (and muscle sugar), in possessing a greater power of overcoming the preliminary acid formed in the presence of glucose or lactose, and in reducing power. The expression "producing gas bubbles" is used here advisedly, since Hesse (vide Lösener) has shown that the typhoid bacillus can produce much gas (CO<sub>2</sub>) though not as visible bubbles. (H<sub>2</sub>S is also evolved.) The eventual alkali formation is dependent upon the amount and kind of sugar, the presence of oxygen, and the initial alkalinity of the medium. If twenty-four hours old cultures of neutral litmus-why are exactly neutralised it will be found that the typhoid and Gärtner bacilli never become acid again, whilst the bacillus coli will form as much acid as it had already done before; although there is still plenty of sugar the two former do not decompose it into acid. Exactly the reverse is the case when cultures in 2.0 per cent. peptone, 0.1 per cent. glucose are neutralised. The great power of alkali production possessed by the bacillus Gärtner is no doubt causally related to the fact that it has a tendency to surface growth. Cobbett has shown that surface growth is necessary for alkali production by the diphtheria bacillus. To the Gärtner group belong the bacilli described by van Ermenghem, Fischer, Gaffky and Paak, Basenau, Cotta, Kaensche, Karlinsky, Günther, &c. Lubarsch has described a bacillus from a newly born child (without data concerning flagella, gas, or indol) which Gärtner reported on as being identical with his bacillus; however, it differs in that it clots milk (vide Gärtner's original description). Petruschky's bacillus faecalis alkaligenes possibly belongs here also, so far I have been unable to obtain a culture to examine, the original description not being sufficiently detailed. The "typhoid" bacilli of certain authors "which have the power of gas production" almost certainly belong here too; also not improbably the cases of "septicemic typhoid fever" described in France, in which "death occurred before typical typhoid lesions had been developed" were in reality due to a bacillus of this group and not to what we recognise as Eberth's bacillus. The different results given in the matter of reducing power are also cleared up to some extent by non-appreciation of this group by the several writers. My observations are quite in harmony with those of Germano and Maurea, in that I have yet to see a true typhoid bacillus which reduces sulphindigotate of soda as rapidly as the bacillus coli does. Another source of difference in the results lies in the constitution of the media, more especially in the presence of sugars, and naturally, also, the contact with oxygen. This I hope to deal with more thoroughly elsewhere.

There is yet one more question which is cleared up on the

<sup>2</sup> I am now quite convinced that this discrepancy is due to faulty staining method, since the culture just received from Dr. Günther, which is described to possess from two to five flagella when stained by Löffler's method, shows from ten to fourteen or more in specimens prepared by that of van Ermenghem. (Specimens were made from fresh four-hour and twenty-hour cultures directly after the receipt of the culture.)

TABLE CONTRASTING THE TYPES OF THE EBERTH, GÄRTNER, AND ESCHERICH GROUPS.

	1. EBERTH GROUP.	2. GÄRTNER GROUP.	3. ESCHERICH GROUP.
Superficial colonies on gelatin plates* ... ..	When typical thin spreading, sulcate; atypical colonies however occur.*	Granular, not sulcate.	May be sulcate or granular; usually rapid spreading.
Rate of growth on gelatin* ... ..	Slow.*	Medium.*	Fast.*
Motility ... ..	Very active.	Very active.	In general less active.
Flagella... ..	10 or more.	10 or more.	8 or less.
Acid produced in neutral litmus whey } after twenty-four hours at 37° C. ... ..	2.5 to 3.5 per cent.†	2 to 3 per cent.	6 to 8 or more per cent.
Ditto, after from four to five days at } 37° C. ... ..	Acid (less than 6 per cent.).	Alkaline (1.5 per cent.).	Acid (more than 10 per cent.).
Nutrient agar or broth with grape or muscle } sugar at 37° C. ... ..	No gas bubbles.	Gas bubbles.	Abundant gas bubbles.
Nutrient gelatin at 18° to 20° C. with grape } sugar ... ..	No gas.	No gas.	Abundant gas.
Media with lactose free from other sugars ...	No gas.	No gas.	Gas.
Litmus neutral solution of 2 per cent. Witte's } peptone and 0.1 per cent. glucose (Capaldi, } Proskauer) after twenty-four hours at 37° C. }	Acid (4.5 per cent.).†	Acid (3 per cent.).	More acid (5 per cent.).
Ditto after several days ... ..	Acid (6 per cent.).	Alkaline (3.5 per cent.).	Alkaline (e.g., 2 per cent.) or neutral.
Bitto eventually ... ..	Generally becomes alkaline.	Alkaline.	Alkaline.
Milk at 37° C. ... ..	Never clotted.	Never clotted.	Clotted in from twenty-four to thirty-six hours.
Reducing power (0.2 c.c. of ½ per cent. indigo- } carmine per 10 c.c. of nutrient agar or } gelatin) ... ..	Slow.	Very rapid.	Moderately rapid.
Potato juice agar‡ at 37° C. ... ..	Scanty translucent.	Rather scanty translucent.	Abundant opaque.
Potato (parallel streak with typhoid bacillus) } twenty-four hours at 37° C. ... ..	Invisible or hardly visible.	Generally just visible.	Abundant yellowish.
Indol formation .. ..	Absent.	Absent.	Present.
Serum reaction with:—potent typhoid serum }	Always positive; extent variable.	Generally positive; but not in high dilution as 1:50,000 or more.	Never positive even in low dilution as 2:100.
“ “ potent Gärtner serum	Rather variable.	Positive, but not universally in the group.	Negative.
“ “ potent “coli” serum	Negative.	Negative.	Variable.

\* Much depends upon the exact constitution of the gelatin, especially the length of time it has been heated (during filtration &c.).

† These figures represent the percentage of 1/10 normal NaOH requisite to neutralise the acidity or of 1/10 normal H2SO4 in the cases where alkalinity is present.

‡ This is prepared by extracting starch-free potato juice (as described by Holtz in the Zeitschrift für Hygiene, Band viii., p. 143) and adding from 1½ to 2 per cent. agar: a clear brown medium results. I find this shows differences better than the clumsy method of “parallel culture.” For purposes of comparison cultures are made upon the same batch of medium.

supposition that Gärtner-like bacilli have been mistaken for those of the other two groups. Demel and Orlandi, amongst others, have stated that animals immunised against the typhoid bacillus are also immune against the bacillus coli. Now according to my experiments, it is clear that the complete sedimentation effect *in vitro* by a given highly diluted active serum is always associated with protective properties when the experiment is made with an animal. Many of those who have ventured to criticise my statements have apparently considered that I hold “agglutinins” and “protective substances” to be identical. That which I have indeed laid stress upon is the fact that sera which have high clumping power also have considerable protective power,<sup>3</sup> but it does not follow from this that sera which have little or no clumping power have also no protective power. Again others have gone further astray and argued that since certain normal, and other non-specific, sera have agglutinating power when in a concentrated condition these sera ought also to possess protective qualities. I must reserve further remarks upon this topic to a paper in which I intend to deal especially with the serum reactions of the bacilli included between typhoid on the one hand and coli on the other; it would be quite useless to draw any inferences on the topic until all the obtainable new races of this class of bacilli react with one or other of the sera in my possession. Although many different kinds of serum are at my disposal (my collection was commenced in 1895) and others will shortly be so, there are still many sera to be prepared. From present experience it is clear that the inquiry on this point must be complete if it is to be of any real value. It will be readily understood that this is no light undertaking. The observation that there are differences between various races of typhoid

bacilli<sup>4</sup> observed *in vitro* has been confirmed by Pfeiffer and Koll *in vivo*. There are also differences in the action of different kinds of typhoid races upon those of the Gärtner group not only in the sedimenting but also in protective effect; in fact these bacilli afford confirmation of the correlation of protecting and agglutinating substances. Those typhoid sera which are efficient *in vitro* have considerable protective power against the two members of Gärtner group which I have tried.

In the accompanying tables of the reactions of sera obtained from typhoid fever patients in different localities three Eberth and two Gärtner group cultures have been used. Typhoid fever (“THS”) has only a very slight mutual serum reaction with Gärtner (“Gärt”), practically none with the Gärtner-like “Ös”; typhoid fever “W” gives (mutually) complete reaction with “Gärt” and distinct with “Ös”; typhoid fever “BW” is intermediate in its action. “Gärt” and “Ös” react mutually in low dilution such as 1:200. The method employed has been practically that of Professor Wright, of Netley, specimens of different dilutions being made in capillary tubes. Having controlled the results given in many parallel observations made by this method with those given by the microscope alone, I venture to assert that his method is by far the most valuable that we are in possession of and on the whole leads to less equivocal results—that is to say, when the criterion of measurement of potency is the ultimate dilution in which reaction can be detected—and for the purposes of testing human sera this is the best criterion. The method I have advocated (finding the least percentage of serum which will completely precipitate a given amount of bacilli at a given temperature in a given time), is of less value in the case of man, because it is not common to find samples which will give “complete”

<sup>3</sup> In fact a reaction of the reaction to infection; but by no means a “reaction of infection” as any experimentalist can demonstrate.

<sup>4</sup> Journal of Pathology, 1896, p. 35.  
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TABLES SHOWING THE REACTIONS OF THE SERA OF PATIENTS SUFFERING FROM TYPHOID FEVER.

In these tables a well marked positive reaction is indicated by +; a slight positive reaction by \*; a trace of reaction by "tr"; doubtful, if any, reaction by ?; negative reaction by 0; and no observation by —.

—		KING'S LYNN.—No. 1.			KING'S LYNN.—No. 2.			KING'S LYNN.—No. 3.		
—		THS.	Gärt.	Ös.	THS.	Gärt.	Ös.	THS.	Gärt.	Ös.
1:20	... ..	+	+	*	+	+	+	+	+	—
1:100	... ..	+	+	0	+	+	0	+	*	—
1:200	... ..	+	?	0	+	tr	0	+	tr	—
1:500	... ..	+	0	0	tr	0	0	+	0	—
1:1000	... ..	tr	0	0	0	0	0	+	0	—
		42nd day: severe attack with relapse.			38th day: severe attack.			End of third week.		

—		MAIDSTONE.—No. 1.				MAIDSTONE.—No. 2.				MAIDSTONE.—No. 3.			
—		TBW.	TW.	Gärt.	Ös.	TBW.	W.	Gärt.	Ös.	TBW.	TW.	Gärt.	Ös.
1:20	... ..	+	+	+	0	+	+	+	0	—	—	+	—
1:100	... ..	+	+	+	0	+	+	+	0	—	+	+	—
1:200	... ..	+	+	*	0	+	+	+	0	—	+	0	—
1:500	... ..	+	+	0	0	+	+	+	0	—	+	0	—
1:1000	... ..	+	+	0	0	+	+	0	0	+	+	0	—
		Six weeks' irregular fever with rigors; clinically doubtful typhoid fever.				45th day: sharp attack; relapse.				Age two years and three months. 34th day: severe attack; relapse.			

—		MAIDSTONE.—No. 6.				MAIDSTONE.—No. 10.				MAIDSTONE.—No. 11.		
—		TBW.	TW.	Gärt.	Ös.	THS.	TW.	Gärt.	Ös.	THS.	Gärt.	Ös.
1:20	... ..	+	—	+	—	—	—	—	—	+	+	—
1:100	... ..	+	+	+	—	+	+	+	*	+	+	0
1:200	... ..	+	+	?	0	+	+	+	?	+	?	0
1:500	... ..	+	+	0	0	*	+	*	0	+	0	0
1:1000	... ..	—	—	—	—	0	+	0	0	+	0	0
		43rd day: relapse.				Typical typhoid fever, 60th day.				30th day: relapse.		

—		MAIDSTONE.—No. 8 (SERUM FROM PUS.			MAIDSTONE.—No. 16.			MAIDSTONE.—No. 13.		
—		THS.	Gärt.	Ös.	HS.	Gärt.	Ös.	THS.	Gärt.	Ös.
1:20	... ..	—	—	—	—	—	—	—	—	—
1:100	... ..	+	tr	0	+	0	0	+	+	0
1:200	... ..	+	0	0	*	0	0	+	*	0
1:500	... ..	*	0	0	0	0	0	*	0	0
1:1000	... ..	?	0	0	0	0	0	tr	0	0
		Pus from glandular abscess undoubted typhoid.			Severe relapse.			26th day.		

—		CLIFTON.—No. 1.				CLIFTON.—No. 2.				CLIFTON.—No. 3.				CLIFTON.—No. 4.			
—		THS.	TW.	Gärt.	Ös.	THS.	TW.	Gärt.	Ös.	THS.	TW.	Gärt.	Ös.	THS.	TW.	Gärt.	Ös.
1:20	... ..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1:100	... ..	+	+	+	*	+	+	+	0	tr	*	*	tr	+	+	+	—
1:200	... ..	+	+	+	0	+	+	*	0	?	tr	?	tr	+	+	+	tr
1:500	... ..	+	+	+	0	*	+	tr	0	0	?	0	0	*	tr	*	0
1:1000	... ..	+	+	*	0	tr	+	0	0	0	0	0	0	tr	tr	?tr	0
		Sent as typical typhoid fever.				Sent as typical typhoid fever.				Sent as typical typhoid fever.				Sent as typical typhoid fever.			

reaction when sufficiently diluted (e.g., 1 per cent.), and observed in columns not less than 1 cm. in diameter; in the diagnosis of bacilli, however, I believe this method to be indispensable. Broth cultures twenty hours old have been used in each case; since "Gärt" and "Ös" both grow more abundantly than the typhoid cultures and also tend to the formation of a pellicle; these were filtered through filter paper and diluted with broth so as to be equally turbid with the typhoid cultures. Extra controls were afforded by specimens (not tabulated) from typical or doubtful cases of typhoid fever which failed to give any reaction with any of the bacilli tried.

In some instances the quantity of serum was not sufficient to give many trials; in others I have reserved some for further testing with other races of bacilli (Dr. Günther, of Berlin, has already most kindly replied to my request for a specimen of the bacillus he isolated). The differences between the samples are of sufficient interest in themselves without waiting for the delay that must ensue before other races of bacilli are to hand.

In these tables, showing the reactions of the sera of patients suffering from typhoid fever, it will be noticed at once that in dilutions lower than and including 1:100 it is immaterial whether true typhoid or Gärtner's bacillus is used to obtain a *typhoid reaction*. In the following cases the Gärtner reaction is stronger relatively, the typhoid reaction being weak or absent.

Cases with Predominant Gärtner Reaction.

	W. AUSTRALIA (Dr. B.). Typhoid fever, December, 1896.				KING'S LYNN, No. 4.			KING'S LYNN, No. 5.		
	THS.	TW.	Gärt.	Ös.	THS.	Gärt.	Ös.	THS.	Gärt.	Ös.
1: 20 ...	0	0	+	+	-	-	-	+	+	+
1: 100 ...	0	0	+	*	0	+	0	+	+	tr
1: 200 ...	0	0	+	tr	0	*	0	*	+	0
1: 500 ...	0	0	0	0	0	0	0	tr	+	0
1: 1000 ...	0	0	0	0	0	0	0	0	?	0

Two cases of undoubted typhoid fever (34th and 27th days) and six doubtful cases reacted negatively to all the bacilli.

Whilst the cases and the races of bacilli are too few to draw any final conclusions it is rather striking that these Lynn and Australian sera exhibit more marked action upon Gärtner's bacillus. I myself had an attack of ill-defined nature (which I thought was typhoid fever at the time) in April, 1896 (immediately after the Wiesbaden Congress) during which I travelled about (in a decrepit condition); about a year ago my serum reacted well on typhoid bacilli in 1:200, six months ago in not more than 1:100 (unfortunately it was not then tested with Gärtner), it then fell to 1:20; a few weeks ago it had no effect upon typhoid but still reacts slightly with Gärtner (1:200). The question naturally arises whether my attack and the W. Australia and Lynn, Nos. 4 and 5 were in reality due to a bacillus of the Gärtner group. To answer this question it is necessary to consider how far the serum reaction is "specific"; already in our earlier observations Professor Gruber and I came to the conclusion that these reactions, as observed with cholera and allied vibrios as well as with the typhoid, Gärtner's and colon bacilli, could not be regarded as truly *specific*; indeed, I suggested that the word *specific* should give place to the word *special*. Since commencing to work at the subject in November, 1894, I have not seen reason to alter my views, for experiments both in vitro and in vivo tend towards the same conclusion. In the diagnosis of bacilli by means of serum reactions it is necessary to have extremely potent samples of serum and to use minute quantities of them. This was laid down originally by Pfeiffer as the result of his animal method, and it is still more true, when the recognition is made by means of clumping and sedimenting effects, as Professor Gruber insisted when he first called the attention of the world to the visible reactions given by typhoid patients' sera. As instances of the marvellous degrees of potency which can be acquired by prolonged (and fortunate) treatment I may state that I have succeeded in getting a sample of "coli serum" which still gave a definite reaction in a dilution of 1 in 2,000,000

on two separate occasions with its own race of coli (the higher dilutions yet tried were 1 in 20,000,000 and 1 in 200,000,000, at which points there was no effect); sera which manifest their presence in 1 in 50,000 to 500,000 are not so difficult to obtain. Now the sera obtained from typhoid fever patients are not potent enough to give absolute indications (in the large majority of the samples I have examined as well as in the above questionable cases) either for diagnosis of bacilli or of the nature of the serum. The results in the tables given above are also evidence in the same direction. So far as I have seen, serum diagnosis in man merely gives an indication of a probability; unless (judging by the effects of extremely potent sera from artificially immunised animals) the reaction is strong in greater dilution than 1 in 1000 (using Wright's method, or 1 in 100 in my own method, macro- and microscopical); microscopical observation alone is not quite so easy, the appearances being often difficult to interpret.

Persistence of the reaction against a given bacillus after it has been lost against allied bacilli is in favour of the original infection having been due to that bacillus.

Since there has been some discussion concerning the length of time that a serum reaction may persist, I would call attention to the fact that several cases are on record in which abscesses due to the typhoid bacillus have occurred five, six, and seven years after the typhoid fever attack. This seems to be more to the point than any discussion on a time limit. Widal has recently published some account of a "para-coli" bacillus from an abscess; his description of the cultural relations and serum reactions are too wanting in precision for discussion here.

Should these lines meet the eye of anyone who has to deal with an outbreak of "meat-poisoning," the clinical course of which may be somewhat typhoid-like according to description, I may say that I shall be more than willing to examine samples of the serum taken from the sufferers; by such means there is a chance of approaching the truth of the matter. Unfortunately all meat-poisonings are not due to Gärtner's bacillus or its congeners.

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CASE OF RHEUMATISM WITH FREQUENT COMPLICATIONS.

BY W. G. DICKINSON, M.R.C.S. ENG., L.R.C.P. LOND., D.P.H.

A MAN, aged twenty-two years, sent for me on the night of Dec. 31st, 1896. He stated that he had not been feeling well for some time, that he had had an attack of influenza about a fortnight previously, and that he now felt much the same as he did then, only worse. He had the usual febrile symptoms, considerable muscular aching, and much prostration. These continued and increased during the next four or five days, the temperature rising to 103.6° F. and the prostration becoming more marked. He was treated at first with twenty grains of salicylate of soda every four hours, but he soon showed great intolerance of this, nausea and severe pain in the back being produced, which ceased when the drug was withheld and returned when it was again tried. On Jan. 5th, 1897, Dr. Hector Mackenzie kindly came to see him. He thought that although there had hitherto been no abdominal symptoms the case would probably turn out to be typhoid fever. No local complication could be