Zeitschrift: Acta Tropica
Herausgeber: Schweizerisches Tropeninstitut (Basel)
Band: 4 (1947)
Heft: 1

Artikel: Bacillary Dysentery
Autor: Weil, A.J.
DOI: https://doi.org/10.5169/seals-310075

(Lederle Laboratories, Inc., Pearl River, New York, U.S.A.)

Bacillary Dysentery.

By A. J. WEIL, M.D.

(Received in original text 22nd October, 1946.) [1]

Necessary limitations of space restrict this review to those aspects of the complex problem of bacillary dysentery wherein important progress has been achieved. It is hoped to show that there is no reason to maintain a fatalistic attitude concerning our ability to restrict the ravages of this disease, which still causes untold losses in well-being and working capacity all over the world, and which is one of the main causes of mortality among children. And this is true even in the U.S.A. with its relatively high standards of sanitation. To cite one single example (1), 14.3% of all deaths of infants under one year of age in the State of Maryland in 1934 were ascribed to dysentery. Morbidity rates in children, and still more in adults, mirror the state of sanitation at a given locality, though this picture is often falsified by highly deficient reports (2). Much too often, even now, diarrhoeic infection is hidden behind euphemistic terms like upset stomach, intestinal grippe and fanciful names like, for instance, "gipsy tummy", as dysentery is often called in the Middle East. Dysentery is just as prevalent in countries of temperate climate as it is in tropical countries if conditions favor it. In other words, incidence and severity of dysenteric infection is not a question of climate but one of economic and sanitary standards. Cleanliness afforded by high levels of private income, and sanitation afforded by high public income from taxation, diminishes the average intensity of infection, and probably the first of the two factors will tend to maintain a high level of resistance by adequate nutrition. Wherever these protective walls of social organization are deficient or weakened, dysentery remains one of the great scourges of humanity. Just as is the case in most other epidemic diseases, it remains true for dysentery that the first step in the combat—once the means for this combat have been provided—is education both of the public and of the medical profession.

The term Shigellosis has been proposed as a more exact description of diarrhoeic infection caused by the genus *Shigella* (3), and

[1] While being printed in this review, the following article has also appeared in French translation in the "Revue d'Immunologie et de Thérapie antimicrobienne", vol. 10, p. 305—327.

this term will certainly serve to educate the medical profession to a more rational diagnosis.

That such education is possible can be seen, for instance, from the statistics in the United States (4) (5). Whereas ten years ago the diagnosis of unclassified dysentery covered nearly 90% of all cases of diarrhoeic infection reported, within recent years these nondescript diagnoses have shrunk to a few percent in favor of an overwhelming majority reported as bacillary dysentery.

Dysentery is a prime example of food-borne infection. All kinds of food can serve as vehicles. Water-borne infection is not part of the classical pattern, although a large-scale outbreak caused by the FLEXNER bacillus that contaminated the water supply of a southern town has recently been described (6). Even sea water near a crowded shore area has been found to contain detectable numbers of viable dysentery bacilli, thus presenting a potential source of infection—for instance, when used for cleaning purposes (7).

Because of the mode of spread, breast fed infants are relatively exempt, and any apparent low incidence in young children has to be considered in the light of the special feeding habits of a given locality. For instance, the low incidence in young children in Japan can be explained by the universal practice of breast-feeding in that country, which is extended over a much longer period of time than is the case in most other countries (8).

From the feces containing dysentery bacilli, the infection is carried to food by two agents; the first is man, and the second is insects, particularly flies (4) (9). Flies have been found to carry dysentery bacilli on their feet, and the possibility that ants may act in a similar fashion when conditions favor such transmission has been suggested by recent experiments (10). The importance of protection of fecal matter, and also of food, against flies is obvious.

Certainly the most important vector under all circumstances, and under good sanitary conditions, the only one is man himself (4). From the epidemiological point of view, the acutely ill and the serious chronic case are of minor importance (11) (12) (13) because they are little involved in the handling of food except under extraordinary circumstances such as occur under war conditions. Of much greater importance is the convalescent carrier. It has been shown that a high percentage of convalescents—at least before the period of universal sulfonamide treatment—carry dysentery bacilli for weeks in a high percentage of cases (8) (11). Moreover, recent investigations have shown a surprisingly high percentage of

carriers among the apparently healthy population. For the city of New York the figure of healthy carriers was found to be 2% and the percentage rose to 3.2 in a large group examined in the states of New Mexico and Georgia, and in Puerto Rico (14). A similar figure has recently been obtained in Chile, where 1.2% of "healthy" carriers of *Shigella* and 0.6% of *Salmonella* were reported (15). The incidence of carriers in military and institutional populations has uniformly been reported to be high (see f.i. [16] [17] [18] [19]). This situation necessitates measures for protection of food from carriers. This is of particular importance in all places where food is prepared centrally, as in barracks and institutions.

It is well to remember that the delimitation of the genus *Shigella* within the large group of *Enterobacteriaceae* is not based on any natural system but on one born of necessity. Scientific classifications, as for instance, that given in BERGEY's Manual (20) tend to hide the weakness of our position. Fortunately, for all practical purposes we have little cause for concern about the theoretical foundations of our classification. We are able to identify all important forms that cause enteric infection without too great difficulty. It is, however, of the greatest importance that we do not hamper progress by a doctrinary attitude.

Before going into the problem of classification and identification of *Shigellae,* it appears useful to mention a few technical points which are of importance for the maximal efficiency of bacterial examination. The use of rectal swabs will in many cases minimize the difficulties of collecting stool samples for mass examination (14). With this method, very valuable data have been collected on the incidence of carriers and of infections in institutions. If laboratory facilities are not immediately available, the transportation of stool samples greatly reduces the percentage of recovery of pathogenic microorganisms. This situation can be considerably improved upon, if small samples of feces are brought into a saline glycerine solution, which simple method prevents overgrowth by other enteric microorganisms (11) (21) (22).

The older media for primary isolations have been greatly improved by two newly devised ones, namely, the desoxycholate citrate (23), and especially the so-called SS agar (24), both of which favor the development of dysentery bacilli im comparison with that of other enteric microorganisms.

Cultural identification by the classical methods remains of paramount importance. However, it has to be realized that cultural variants are frequent. Even the importance of the old distinction between mannitol fermenting and non-mannitol ferment-

ing is subject to exemption. Thus non-mannitol fermenting FLEXNER strains have been found not so very rarely (vide infra and [25]).

From recent investigations (26) on the nutritional requirements of *Shigellae,* synthetic media have been developed which often can be used with advantage, for instance, when it is important to avoid the antigenic components of the usual media (27) (28).

A valuable addition to methods of differentiation has been provided by WOOD's observation that among the pathogenic *Shigellae,* the SHIGA, SCHMITZ, and FLEXNER bacilli do not reduce trimethylamine oxide, whereas the SONNE bacillus, and *Sh. alkalescens* (and also *Sh. dispar*) are able to reduce this compound (29) (30). Besides the dispar bacillus, many coliforms reduce this compound, and therefore, the inclusion of the WOOD test in the routine of cultural tests of suspected strains provides an additional safeguard against diagnostic errors.

The essential properties of those species of *Shigella* for which satisfactory proof or pathogenicity in man has been given are presented in Table I.

In the following, we list them under the names which are most widely accepted, and the designation given in BERGEY's Manual (20):

a) The SHIGA bacillus *(Sh. dysenteriae),* the prototype of the genus. It is antigenically homogeneous. It is indol-negative and does not form acid from mannitol.

b) The SCHMITZ bacillus *(Sh. ambigua).* It was first observed in Macedonia during World War I. Subsequently, it has been found to be present all over the world, and is certainly not less frequently found than the SHIGA bacillus. Under present conditions, it is widely distributed in the United States, both in outbreaks and sporadically (see for instance [18]). Culturally it is distinguished from the SHIGA bacillus by its ability to form indol and to acidify rhamnose (isodulcitol). It is also antigenically homogeneous.

c) Several serological and cultural types of non-mannitol fermenting bacteria have attracted attention in recent years following a paper by SACHS (31) from India. These types are usually referred to as SACHS group though the essential observations had previously been published by LARGE (32). Five types which are designated as Q 454, Q 771, Q 902, Q 1030, and Q 1167 (Q for Quetta, India) are culturally typical *Shigella* (33) (34), and a reasonable amount of evidence concerning their pathogenicity has been accumulated, particularly from findings in the Middle East and the Mediterranean area (25) (35) (36). They have also been

recently reported from the U.S.A. (33), West Africa (60), and New Guinea (25). The position and pathogenicity of several other forms described by SACHS is still in doubt both as to their pathogenic and cultural properties: they either form abundant gas or are motile (33) (34).

Another mannitol non fermenting bacillus connected with diarrhoeic infection has since been reported from Wakefield in England (37), which we are inclined to think is a *Shigella* (38) (though this opinion is not generally shared [39]). One investigator even found such strains motile (33). However, this finding was not duplicated elsewhere (37) (38) (39). *Shigella* Wakefield shares a heat labile antigen with type Q 454 of LARGE and SACHS (38).

TABLE I.

Main Differential Characteristics of Dysentery Bacilli.

Species	Motility	Indol	Wood's Test	Gas-formation	Glucose	Lactose	Mannitol	Dulcitol	Rhamnose	Arabinose	Serological Behavior
Sh. dysenteriae (Shiga)	—	—	—	—	+	—	—	—	—	—	Uniform
Sh. ambigua (Schmitz)	—	+	—	—	+	—	—	—	+	– or +	Uniform
Large-Sachs group	—	– or +	—	—	+	—	—	– or +	– or +	– or +	5 Types
Sh. paradysenteriae (Flexner)	--	– or +	—[1]	—[2]	+	—	+	—[2]	—[3]	+	19 Types
Sh. sonnei	—	—	+	—	+	+ (late)	+	—	+	+	2 Serologically Different Phases
Sh. Alkalescens	—	+	+	—	+	—	+	+	+	+	Uniform (Common Form)

1 Shigella etousae is Wood positive.

2 Type VI strains of the Newcastle variety form slight amounts of gas and acidify dulcitol.

3 Some strains acidify rhamnose, particularly type III.

d) The FLEXNER bacillus *(Sh. paradysenteriae).* The former division into sub-species according to minor variations in fermentation of carbohydrates has now been generally abandoned as meaningless. The species includes a group of bacteria that form small amounts of gas and which had been designated as NEWCASTLE (non-mannitol-fermenting) and MANCHESTER (mannitol-fermenting) bacilli (40) (41) (42). BOYD (43) (44) has shown that these forms are antigenically identical with typical FLEXNER strains, and proposes to include all forms in one of his types (VI). His observations have been confirmed (27) (45), and the various cultural variants are now rather generally referred to as type VI of FLEXNER.

It has been recognized since KRUSE's investigations that the FLEXNER bacillus is antigenically heterologous. Considerable efforts have been made to explore the antigenic peculiarities of the FLEXNER bacillus. The most important work in this direction has been done by ANDREWES and INMAN (46), who differentiated four independent antigens, each of which predominates in one race; these they proposed to call V, W, X and Z. A fifth race "Y" was supposed to contain all these antigens in nearly equal amounts. Subraces with two primary (predominant) antigens were recognized as subraces VZ and WX. ANDREWES and INMAN (46) were fully aware that that was not the whole story and subsequent investigations show that their schema covered only about two-thirds of the strains found (31) (44) (47) (and many others). This unsatisfactory state of affairs remained unchanged until BOYD (43) (44) took advantage of the large material at his disposal at his laboratory in the Indian Medical Service to re-examine the whole problem. He found nine additional types, one of which includes the gas-forming NEWCASTLE and MANCHESTER strains mentioned above. The main results were repeatedly confirmed (27) (45). The whole problem was re-investigated in our laboratory. According to our findings (27) each type is characterized by a predominant antigen for which the designation of primary antigen according to ANDREWES' and INMAN's original suggestion has been retained. And it has been established that these "primary" antigens dominate the immunological response of the host (48) (49) (50). The five "races" of ANDREWES and INMAN (of which BOYD had questioned the existence of two) and the nine types described by BOYD can be labelled by one such primary antigen each.

During the war years an additional type of the FLEXNER bacillus has been found in England, France, and Italy (51) (52) (53) which is usually designated as *Sh. etousae* (from the European Theatre of Operations, U.S. Army) or LAVINGTON I. The only cultural deviation from the FLEXNER type is that these strains are able to reduce trimethylamine oxide to trimethylamine.

Thus, fifteen types with single primary antigens can be distinguished by a schema basically similar to that of the KAUFMANN-WHITE schema for the o antigens of *Salmonellae*. The types are numbered according to their primary antigen. The network of cross reactions was traced to antigens, secondary in the respective types, most of which have been presently identified as serving as primary antigens in other types. In addition—also in confirmation of ANDREWES' and INMAN's classical work—types have been shown to exist which have two primary antigens; four of these

dual types have now been recognized with certainty (27) (54). Thus, the following schema of classification has been proposed (Table II).

TABLE II.

Classification of the Flexner Bacillus.

According to Primary Antigen (Weil, Black & Farsetta (25) (54)	"Race" of Andrewes & Inman (46)	Correspondence with Classification of Boyd (41)
I	V	Flexner I
II	W	Flexner II
III	Z	Flexner III
IV		Flexner IV (Boyd 109)
V		Flexner V (Boyd 103)
VI		Flexner VI (Boyd 88-Newcastle-Manchester)
VII	X	
VIII	Y	
IX		Boyd I (170)
X		Boyd II (288)
XI		Boyd III (D 1)
XII		Boyd D 19
XIII		Boyd P 143
XIV		Boyd P 247
Etousae		
I, III	VZ	
III, IV		
II, VII	WX	
V, VII		

It was found that sera stripped of their secondary (crossing) antibodies by appropriate absorption can be employed expediently for routine identification of types. Such typing can be conveniently done by means of slide agglutination (27). Such sera are now being used widely; for instance, in the medical services of the United States Navy (47), and the United States (56) and British Armies. They have now also been made available for general laboratory use by Lederle Laboratories, Inc., New York, N.Y. The practical advantages of the procedure are evident.

Data on the incidence of the various species and types of *Shigella* are of primary importance for our knowledge of the immunological situation in infected human beings. As mentioned before, the primary antigen is one which dominates specificity of protection both experimentally in the chick embryo (48), in the mouse (49), and in man (50). It is obvious that any attempt to protect specifically by vaccination against the infection with this most prevalent species of *Shigella,* has to take into consideration

TABLE III.

Exemplifying the Incidence of Flexner Types.

TYPES Andrewes-Inman-Boyd			I	I III	II	II VII	III	VII	VIII	III IV and IV	V	VI	IX	X	XI	XII	XIII	XIV	Etousae	Reference
			V	VZ	W	WX	Z	X	Y	103	P119	88[2]	170	288	DI	D19	P243	P274		
Year	*Country*	*Specimen*																		
1943/44	USA - South-eastern States	709[1]	3.1	×	26.9		3.2	10.1	2.1	1.6	0.1	52.5	0	0.2	0	0	0	0.1	×	19
1944	USA-Michigan & New Mexico	142	46.5	×	25.4	×	7.0	0	2.8	9.2	2.8	5.6	0	0.7	0	0	0	0	×	55
1943/44	USA-California	161	35.4	×	0.6	×	5.6	×	×	18.7	5.6	8.7	4.4	1.9	1.9	7.4	2.4	7.4	×	58
1946	Brazil - Rio de Janeiro	79	6.3	23.9	21.3	5.1	23.8	1.3	6.3	1.3	0	5.1	0	2.6	1.3	0	0	1.3	×	59
1944/45	France	1847	4.8	×	3.3	26.8	6.6	6.6	0	2.6	1.7	46.7	0.5	0	0	0	0	0	0.5	16
1932/35	India	4800				77				4	2.5	7.5	4	1.5	1.5	0.2	0.3	1.5	×	44

× not mentioned in publication [1] entirely or predominantly military personnel [2] Newcastle, etc.

the type specificity of protection, and disregard of this point may explain the unsatisfactory results of many former attempts at active immunization. Thus, for the sake of progress in our knowledge of the epidemiology of dysentery, and for the development of specific protection, it will be most important to obtain reliable data on the incidence of FLEXNER types all over the world. Few such data are available at present; typical examples are given in Table III. A few types cover the large majority of the cases; namely, types I, II, III, VI, and I. III. Also type IV has been found to be quite frequent in some localities as for instance in Puerto Rico (57). The incidence of any type may vary greatly from one locality to another, as is evident from the examples described in Table III.

Cross relations between several of the FLEXNER types and other species of *Shigella* and also of *Salmonella* are known to exist (33) (61) (62) (63) (144) (145). They are caused by minor antigens and are of no practical importance, if properly absorbed sera are routinely used.

The antigenic relation within the genus FLEXNER (and also the phase variation of the SONNE bacillus, which will be considered presently) has to be kept in mind, if reliable results are expected from WIDAL tests. However, the peculiarities of dysenteric infection make the test for antibodies in the patient's serum far less important for routine diagnosis than is the case in *Salmonella* infection.

Some types of FLEXNER bacilli show a peculiar variation in serological behavior (44) (64), which is probably a phenomenon similar to that observed in the SONNE bacillus (vide infra), and of which the only parallel known elsewhere in bacteriology is possibly the phase variation of *H. pertussis*. Namely, when kept for any length of time on artificial media, there appears an antigenically different phase. These phases are designated as phase A (for the original) and phase B (for the variant). At least in the FLEXNER bacillus type IV, the antigen of the second phase corresponds closely to the complex secondary antigen of phase A. This phase variation is independent of the classical smooth-rough variation.

Furthermore, FLEXNER bacilli may possess in addition to the heat stabile antigens, heat labile ones which remind in their behavior of the Vi antigen of the typhoid bacillus (65) (38). Such antigens may impair or inhibit agglutination by sera versus the heat stabile antigen. BRAUN (in Instanbul) found a number of cases where the heat labile antigen was highly antigenic. Unfortunately, the restrictions imposed by the War made contacts with the workers very difficult. Thus at the present time it is not known

which serological types of the FLEXNER bacillus were involved in his work. In our own experience, we found it difficult to obtain evidence of antigenicity for heat labile material in FLEXNER bacilli, though we (38) were able to demonstrate a highly antigenic heat labile antigen in the WAKEFIELD bacillus which, as mentioned before, is shared by *Shigella* Q 454.

It has been known for many years (66) that SHIGA bacilli may be inagglutinable or poorly agglutinable by the homologous serum. Similar observations have subsequently been made independently in various laboratories on ambigua, alkalescens, FLEXNER types VI, IX, X, XI, XII, XIII, XIV and the Q strains described in India (27) (38) (67). This inhibition can be removed by boiling the cultures for ½ to 1 h. Heated bacteria are, therefore, not so rarely needed for the differentiation of *Shigellae* by serological methods. The inhibiting substance is evidently very weakly, if at all, antigenic. (For the case of the *Shigella* bacillus, presumptive evidence has been obtained recently [68] that a heat labile antigen can be obtained by extraction with urea. Whether this is true for other *Shigella* remains to be seen.) That the inhibiting substance is not necessarily identical with the heat labile antigen could be clearly demonstrated for the case of Q 454 (38).

e) The SONNE bacillus (Sh. sonnei) is characterized by slow acidification of lactose, which places this species in an exceptional position among the pathogenic *Enterobacteriaceae*. Observations up to three weeks are necessary to definitely exclude such reaction.

Thus, differentiation between the SONNE bacillus and FLEXNER bacillus by cultural methods is very time-consuming, and the difference in ability to reduce trimethylamine oxide provides a most welcome means of differentiation within twenty-four hours (29) (30).

The SONNE species is in itself antigenically homogeneous. There is, however, a peculiar phenomenon to be considered. The SONNE bacillus shows a phase variation which is not to be confused with the classical smooth-rough variation. This variation occurs within the limits of what, according to the usual definitions, has to be called the smooth state; that means both phases are, for instance, salt stable. The phase variation is characterized by differences in colony form; the first phase forms round colonies with smooth surfaces, whereas the second phase is characterized by irregular rims and granular surface. At the same time a change in antigen occurs. Thus, phase I is antigenically completely different from phase II. The factual observations are related in many old reports (see for instance [69] [70]), but its biological significance has been clarified only recently (71).

Both phases occur on primary stool plates; and in the infected individual antibodies against either one or both phases may be found. It is obvious that the serological diagnosis is possible only if sera are available that contain antibodies against both phases.

On culture on artificial media, most SONNE strains have a tendency to change from phase I to phase II; reversion from phase II to phase I has been described (72), but we have no means of effecting it with regularity, and no observations have been recorded which would point to such a reversion on artificial media.

Even though the SONNE bacillus causes, in the average case, a mild form of dysentery, it would be erroneous to generalize in this respect. For instance, 40% of severe dysentery in Japan ("Ekiri") is caused by the SONNE bacillus (8).

f) *Bacillus alkalescens (Sh. alkalescens)* was originally described by ANDREWES merely for the sake of its differentiation from the FLEXNER bacillus. Only in recent years, evidence has been brought forward which allows us to assert its pathogenic nature (73) (74) (75) (76). It is found relatively frequently in the urine as a causative agent of cystitis and pyelitis. It occurs relatively frequently in the feces as a mere commensal, and thus discovery in fecal cultures can be accepted as proof of its etiological relationship only with some reservations, and confirmation by repeated isolation, WIDAL test, etc. is desirable.

B. alkalescens as it ordinarily occurs presents a serologically uniform pattern, in which several antigens can be distinguished (77). However, one antigenically different form has been described in Brazil (78) (79) and two more have been found recently in the United States (80). These types II to IV will need further investigation in order to establish their position.

Species closely related to the SONNE bacillus, differing mainly in that they form indol, have been described as *Bacillus ceylonensis* and *madampensis,* and as *Bacillus dispar,* which will best be grouped together according to present knowledge as *Shigella dispar,* of which *madampensis* and *ceylonensis* present two of several types (81). Pathogenicity for this species has often been claimed, but no satisfactory evidence has yet been presented that it is actually able to cause diarrhoeic infection. Further investigation of this point is desirable.

In table IV, we present a collection of representative data on the incidence of *Shigella* species: in the forefront stand the FLEXNER bacillus and SONNE bacillus; the latter gains prominence if all cases of diarrhoeic infection, and not only the more severe ones, are considered in the statistics. Conversely, wherever a thorough study of the situation has been made, the SHIGA bacillus appears to be com-

TABLE IV.

Exemplifying the Incidence of Shigella species (per cent).

Year	Country	Specimens	Shiga	Ambigua	Large-Sachs Group	Flexner	Sonne	Alkalescens	Others or unclassified	Reference
1936/39	U.S.A., New Mexico	2081	0	×	×	81	19	×	×	82
1937/40	U.S.A., Mississippi	760	2	2	×	81	15	×	×	83
1943/44	U S A., South Eastern States	2113[1]	0	1	×	33	62	3	0.1	19
1940/42	Uruguay	393	0	2	×	89	9	×	×	84
1937	Scotland (Glasgow)	608	0	0	×	56	44	×	×	85
1927/29	Denmark	988	0	0	×	25	75	×	×	11
1928/29	Germany-Silesia	1156	0.4	×	×	69	31	×	×	86
1942	Germany	7071	0.9	×	×	13	86	×	×	87
1944/45	France	191[2]	0	1.5	0.5	92	2.5	3.5	×	16
1942	German Eastern occupied country (Poland?)	2265	4	×	×	95.5	0.5	×	×	87
1928/29	Egypt	392	13	4	×	73	10	×	×	88
1943/44	Egypt	279[1]	2	8	7	54	20	2	7	36
1940/42	Middle East	17801[1]	18	7	2	62	7	×	4	25
1932	India	687	10	6	5	64	14	×	1	32
1932/35	India	7339	14	6	×	65	11	×	4	43
1938/41	India	9777	11	7	0.5[3]	65	16	×	0.1	31

× not mentioned in report

1 entirely or predominantly military personnel

2 U.S. Army personnel and German prisoners of war

3 7% in Quetta (where special attention was given to this group)

paratively rare and so are the other members of the non-mannitol-fermenting species, such as the SCHMITZ bacillus. On the whole, the SCHMITZ bacillus is found somewhat more frequently than the SHIGA bacillus. Our knowledge of the relative importance of *Sh. alkalescens* is too incomplete to permit us to draw any conclusions as yet. It would be highly desirable to have more data on the incidence of species and types of *Shigellae,* and this task will be greatly facilitated by the new technique of typing (27) (56) (148). The incidence of the non-mannitol-fermenting bacteria of the group of LARGE and SACHS also remains to be determined; at the present stage of our knowledge they too seem to play nowhere a predominant part.

Single strains with independent antigens have been found (25) (33) (89), and additional ones are likely to turn up from time to time just as is the case with *Salmonellae.* However, it appears that our present knowledge of types covers adequately the overwhelming majority of *Shigellae* wherever this problem has been studied with modern methods of cultural and serological investigation.

Diarrhoeic infection can, of course, be caused by any member of the genus *Salmonella* that is pathogenic for man, including the typhoid bacillus. Severe clinical infection with *Salmonella* will be clinically distinctly different, but slight infections are often clinically indistinguishable. From what is known at the present time, diarrhoeic infection by *Salmonellae* represents, as a rule, only a small percentage of the total cases of acute diarrhoea. However, investigators in Uruguay (90) have detected one case of *Salmonella* to each two cases of *Shigella,* and it will need further studies to decide whether similar high percentages are found elsewhere, and the peculiar conditions which make for such high percentages of diarrhoeic infection due to *Salmonellae;* at present, evidence indicates the contrary ([3] and others).

Bacilli of the paracolon and of the proteus groups, particularly *Proteus morgani,* have been accused of causing diarrhoeic infection, especially in small children. Intestinal infection due to these bacteria is probably as a rule restricted to very special conditions, particularly where there is weakened resistance by other disease or malnutrition. However, there are no a priori reasons why certain strains of "apathogenic" *Enterobacteriaceae* may not occasionally develop properties resembling those of pathogenic ones. Recent observations (91) (92) invite further investigation of this problem.

In this respect, it is of interest to note that rhesus monkeys are particularly prone to contract FLEXNER dysentery when the water-soluble vitamin "M" is lacking (93) (94) (95) (96). Recent investigations have made it appear likely that this vitamin is identical with

the *Lactobacillus casei* factor (vitamin B_c, "folic acid") of the vitamin B group (97) (98). Though folic acid plays a definite role in sprue with its characteristic intestinal disturbances, there are no definite indications for a relation of this vitamin to susceptibility of man for intestinal infection; but it would be worth while to give this point further attention. It has long been known that resistance to enteric infection is subject to wide variation, and exhaustion and malnutrition have often been implicated without our being able as yet to point to any definite causal nexus. The close relationship of war, and other violent disturbances of social stability, with epidemics of dysentery will be recalled in this connection.

It is not possible, at this time, to discuss the clinical picture of dysentery. A comprehensive presentation of the clinical aspect can be found in (5). It may be worth while to note here that dysenteric infection must not necessarily be connected with diarrhoea as the predominant symptom. Slight infections are sometimes marked only by a rise in temperature and vomiting. Dysentery can be masked behind the clinical appearance of appendicitis, meningitis, and pneumonia (99). The proper diagnosis of these masked forms is of considerable epidemiological importance because it contributes to the chain of infection if they are not properly dealt with.

The immunological specificity of *Shigella* depends upon its somatic antigen. It is thought that this antigen is a surface antigen. Considerable investigational work has been done to elucidate its structure. We know that its specificity depends upon a high molecular polysaccharide. However, the isolated polysaccharide is in itself not antigenic. In order to become antigenically effective, it must be used in the complete form as it occurs naturally; namely, coupled to a polypeptide and a lipid. References to isolation, antigenicity and structure will be found in (14), (see also [100] [101]). The specific polysaccharide is present only in the smooth variant. Rough forms contain a polysaccharide of their own which is antigenically rather nonspecific. About the proteinic and nucleoproteinic constituents that represent the bulk of the dry weight of the bacteria, relatively little is known (100). The protective antibody in rabbit serum is essentially identical with and that versus the specific polysaccharide (102).

All *Enterobacteriaceae* are definitely poisonous in the sense that killed bacteria in amounts of the order of milligrams kill white mice, and slightly larger amounts are fatal for rabbits (100) (further references in [4]). This toxicity is accounted for practically 100% by the complete antigen which represents roughly 10% of the total bacterial weight and which, when isolated, is about ten times more toxic by weight than are whole bacteria. The poly-

saccharide and the other fractions of the complete antigen are not toxic. However, it has recently been claimed (100) that the polysaccharide and the polypeptide could be obtained in a toxic form. If this is the case, it would suggest that toxicity is associated with a still unknown fourth component of the complete antigen. The complete antigen has a very characteristic effect on temperature regulation, blood sugar level, and output of leukocytes, and it causes hemorrhagic lesions (103 to 105). It appears possible that the adrenal system may be the primary point of attack.

The effect is neutralizable by the specific antibody but only in low multiples (106), which would be expected. These experimental data on the toxic effect of the somatic antigen go far to explain certain features of the pathology of enteric infections (106). However, we have no information whatsoever regarding the factors which constitute what is usually called virulence. In other words, we do not know what enables the typhoid bacillus, for instance, to maintain itself inside the body, or what the difference between saprophytes like the colon bacillus, and *Shigellae* is that enables the latter to invade the intestinal wall. We have good reason to believe that disease is caused only if bacteria migrate through the mucosa. In other words, their presence in the lumen of the intestines is not enough to cause disease. The characteristic ulcerations of the intestines are caused by damage inflicted within the intestinal wall (107) (108). FLEXNER (107) has compared the toxic effect with that of heavy metals which also enter the intestinal wall, although in the latter case the process is concerned with secretion from the blood stream.

Toxic substances other than somatic antigen have not been found in most members of the various *Shigellae*. The only exception is the SHIGA bacillus which forms an exotoxin which has a characteristic effect on the nervous system, whence this exotoxin has also been termed "neurotoxin" (106). The exotoxin of the SHIGA bacillus is a true toxin like that of diphtheria and tetanus. An antitoxin which neutralizes the toxin in high multiples is formed in response to its introduction into the animal body. Formation of antitoxin has also been demonstrated in man (109). Nevertheless, we do not know the precise role, if any, of the SHIGA exotoxin in clinical infection. The simple consideration that the clinical disease caused by the SHIGA bacillus is similar to that observed in infections with the majority of *Shigellae* that do not form a true exotoxin, shows that the pathology of dysentery is not that of a poisoning with exotoxin, as is the case in diphtheria. No conclusive evidence has been given of the therapeutic effect of SHIGA antitoxin. In this connection, it is to be remembered that all antitoxins

contain also antibacterial—that is, antisomatic—antibody which, as has been mentioned before, is the carrier of the specific immune response (102) (106). For minor antigenic components of dysentery bacilli, see references in (4).

Experimental work with *Shigella* had been hampered in the past by the lack of a suitable experimental animal. The mucin method in the mouse, so helpful in many other experimental studies, has also proven to be applicable to infection with *Shigella* (49) (110). However, not all strains are pathogenic to the mouse even with mucin, and this somewhat restricts the value of the method.

Many smooth *Shigellae* are highly pathogenic for the chick embryo (111), and with appropriate technique this method is very convenient for studies on passive protection (48) (49) and also for chemotherapeutic experimentation (112) (113).

(To be concluded.)