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Some studies on the epidemiology of Sonne dysentery. Changes in colicine type and antibiotic resistance between 1956 and 1965

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INTRODUCTION

The epidemiology of Sonne dysentery presents a number of problems. In large urban areas the infection is endemic and it spreads, in larger or smaller epidemic episodes, to smaller areas of population. The infecting dose is small and infection is principally transmitted by direct or indirect contact (Hutchinson, 1956); food-borne outbreaks are uncommon. There is a well-marked seasonal variation in frequency with a peak in the early spring (Bradley, Richmond, Shaw & Taylor, 1958) and there is no obvious immunity following infection. It was hoped that the use of colicine typing (Abbott & Shannon, 1958; Abbott & Graham, 1961) and the further characterization of strains of *Shigella sonnei* that was possible by determining their antibiotic sensitivities might throw light on the spread of Sonne dysentery by enabling one to follow accurately the spread of infection from individual to individual.

Recent work has shown that the factors responsible for antibiotic resistance and for colicine production may be transferred from organisms possessing these properties to others that lack them. This transfer is not confined to members of a single species but can occur between organisms of many genera within the family Enterobacteriaceae (Datta, 1962; Watanabe, 1963; Ozeki, Stocker & Smith, 1962).

Anderson & Lewis (1965) have shown that an organism might carry a transfer factor, a resistance determinant, both, or neither. Organisms possessing both the transfer factor and a resistance determinant were able to convert a proportion of suitable sensitive organisms to resistance. Organisms carrying the resistance determinant alone were resistant to the antibiotic but unable to transfer this resistance unless it was mobilized by a transfer factor from some other source. Sensitive organisms carrying the transfer factor alone infected a high proportion (10–50 %) of other organisms with this factor without changing their resistance. Ozeki *et al.* (1962) showed that some factors responsible for colicine production could be transferred to strains that lacked them, and Anderson & Lewis (1965) found that the transfer factors responsible for the transfer of antibiotic resistance and for colicine transfer were mutually replaceable.

Usually resistance or colicine factors were transferred only to a small proportion (*ca.* 1/1000) of susceptible cells but Anderson & Lewis (1965) describe two resistance determinants which were not separable from the transfer factor and which infected—and gave resistance to—a high proportion (*ca.* 50 %) of susceptible cells.

The factors *Col 1* and *Col B* of Ozeki *et al.* (1962) could also be transferred to a high proportion of susceptible cells and such transfers clearly could change the character of an intestinal organism in the absence of special conditions (e.g. antibiotic therapy) favouring the organism with newly acquired characters.

A few experiments in our laboratory have shown that both antibiotic resistance (to sulphonamide, streptomycin and tetracycline) and colicine production can be transferred to strains of *Sh. sonnei* from strains of *Escherichia coli* derived from normal faeces possessing these properties and from *Sh..sonnei* to susceptible strains of *E. coli*. The exact details have not yet been worked out but it seems likely that they will conform to the model described by Anderson & Lewis (1965).

METHODS AND MATERIALS

Source of materials

Specimens of faeces were received for bacteriological diagnosis from General Practitioners and Medical Officers of Health in the London area. The home address of the patient made it possible to assign each isolation to a Local Authority area but the source of infection might have been elsewhere. Approximately 90 % of the isolations of *Sh. sonnei* were derived from fifteen boroughs, namely, Islington, Hackney, Stoke Newington and Shoreditch in North and North-East London, Chelsea, Kensington and Hammersmith in West London, Wandsworth, Battersea, Lambeth, Camberwell, Southwark and Bermondsey which made up the whole of the London County Council area south of the River Thames and two county boroughs outside the central area, West Ham and Croydon. The remainder of the isolations were derived from a number of other boroughs in Central London but specimens were not received regularly and in large numbers from them over the whole period of observation. Some of the analyses of the results have been confined to the fifteen 'major' boroughs. No specimens were examined from Bermondsey during the first 18 months of observation nor from Croydon during the last 12 months. The results obtained from large residential institutions in which Sonne dysentery was often endemic for long periods have not been included.

In October 1956 Dr J. D. Abbott made available to us his method of colicine typing and sent us his indicator strains. This enabled us to start routine colicine typing before the method was published and we are extremely grateful to him for this courtesy.

On 1 April 1965, the administrative structure of London was reorganized, with the merging of boroughs and changes in boundaries. This seemed an appropriate moment to conclude this particular series of observations.

Isolation and identification of Shigella sonnei

Specimens of faeces were plated on deoxycholate citrate agar and inoculated into selenite broth which was plated on the same medium after 24 hr. incubation. Identification of *Sh. sonnei* was based on preliminary slide agglutination followed by biochemical and serological confirmation.

Selection of strains of Shigella sonnei *for further investigation*

It was not possible to investigate the resistance pattern and colicine type of every strain isolated since the numbers were too great. No strains from convalescent patients, i.e. those known to have been previously infected, have been examined. So far as fresh infections were concerned, our policy has been to investigate one strain from each incident—an incident being defined as a number of infections that might be expected to have a single source. In practice this has meant that one strain has been investigated from infections in families, in day nurseries and in small residential institutions. In fact, we have often examined several strains from larger outbreaks in day nurseries but, in order not to load the results, only the first strain has been included in this analysis. It has not always been possible to examine every strain from sharp outbreaks in primary schools but otherwise we have been able to maintain our policy of examining one strain from each incident.

Tests for sensitivity to antibiotics

A single colony was picked from the primary deoxycholate citrate plate into peptone water containing 1 % of lactose and sucrose and an indicator, and on to an agar slope. After the peptone water cultures had been incubated for 4–6 hrs. at 37° C., sensitivity tests were put up by streaking small loopfuls of culture, usually 8 to a plate, to a single disk in the centre containing the appropriate antibiotic. Tests for sulphonamide sensitivity were carried out on lysed blood agar plates to a disk containing 300 μg. sulphathiazole; tests for sensitivity to streptomycin and terramycin on nutrient agar plates to disks containing 25 and 50 μg. respectively. Tests were read after overnight incubation and checked for purity. Neomycin has been used throughout this survey but only occasional strains have been found resistant to it. Ampicillin and chloramphenicol have been used from time to time; about 50 % of strains were resistant to the former, occasional strains to the latter.

Colicine typing

The method did not differ materially from that described by Abbott & Shannon (1958), in which the strains of *Sh. sonnei* were grown on tryptose soya agar (Oxoid) containing 5 % horse blood and nine indicator strains were used to detect colicine production.

We have found that the colicines produced by some strains of *Sh. sonnei* are somewhat thermolabile and may be partly destroyed by incubation, as recommended by Abbott & Shannon, for 3 days at 37° C. Maximum colicine production appears to occur after overnight incubation at 33–35° C. and this temperature is to be preferred.

Our experience agrees with that of Abbott & Graham (1961) that colicine type 11 should not be separated from type 6. When incubated at 33–35° C., all strains of type 11 have given the inhibition pattern of type 6. During the course of this work we have isolated five strains of *Sh. sonnei* whose inhibition patterns did not allow them to be assigned to any colicine type. Since each occurred once only, they have been excluded from this analysis.

RESULTS

During the 8½ years under review (October 1956 to March 1965) *Sh. sonnei* was isolated from 19,859 infected persons. The results of colicine typing and antibiotic resistance of 9419 of these strains are analysed here on the basis of one strain from each incident as previously defined. In a large urban area, such as London, the total incidence of Sonne dysentery is made up of the sum of several local prevalencies. We have often observed the rise and fall of local epidemics; sometimes these have been isolated events in the sense that there was no increased frequency of infection

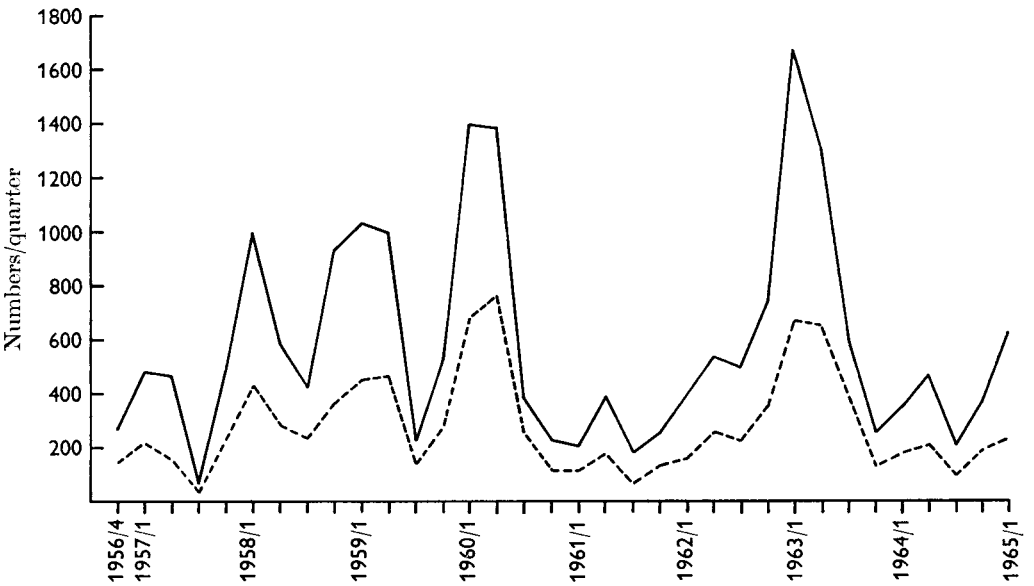

Fig. 1. The quarterly number of incidents and new isolations of *Sh. sonnei*, 1956–65. ——, New isolations; - - -, incidents.

elsewhere, at other times local epidemics of varying severity have occurred more or less simultaneously in several areas. In each of the fifteen boroughs from which large numbers of specimens have been regularly examined, the highest number of new infections in any one quarter has been at least 30 times, and in several boroughs 100 times, greater than the lowest quarterly total of new infections.

The number of incidents and the total number of new isolations of *Sh. sonnei* from October 1956 to March 1965 for each period of 3 months (quarter) are shown in Fig. 1.

This figure shows a series of winter peaks and summer troughs—the usual distribution of Sonne dysentery in Great Britain at the present time. In some winters there was little real increase in the incidence of dysentery. It will also be seen that the ratio of incidents to new isolations remained roughly constant throughout the observation period.

The distribution of colicine types is shown in Fig. 2 by 3-monthly periods over the 8½ years that observations have been made. Strains of *Sh. sonnei* that produce

no detectable colicines are described as type 0 by some workers and 'untypable' by others. Attempts, since the original description of the technique by Abbott & Shannon (1958), to demonstrate colicine production by these strains have all proved fruitless and it has not proved possible to divide up this group in other ways. It seems that these strains are best regarded as producing no colicines and

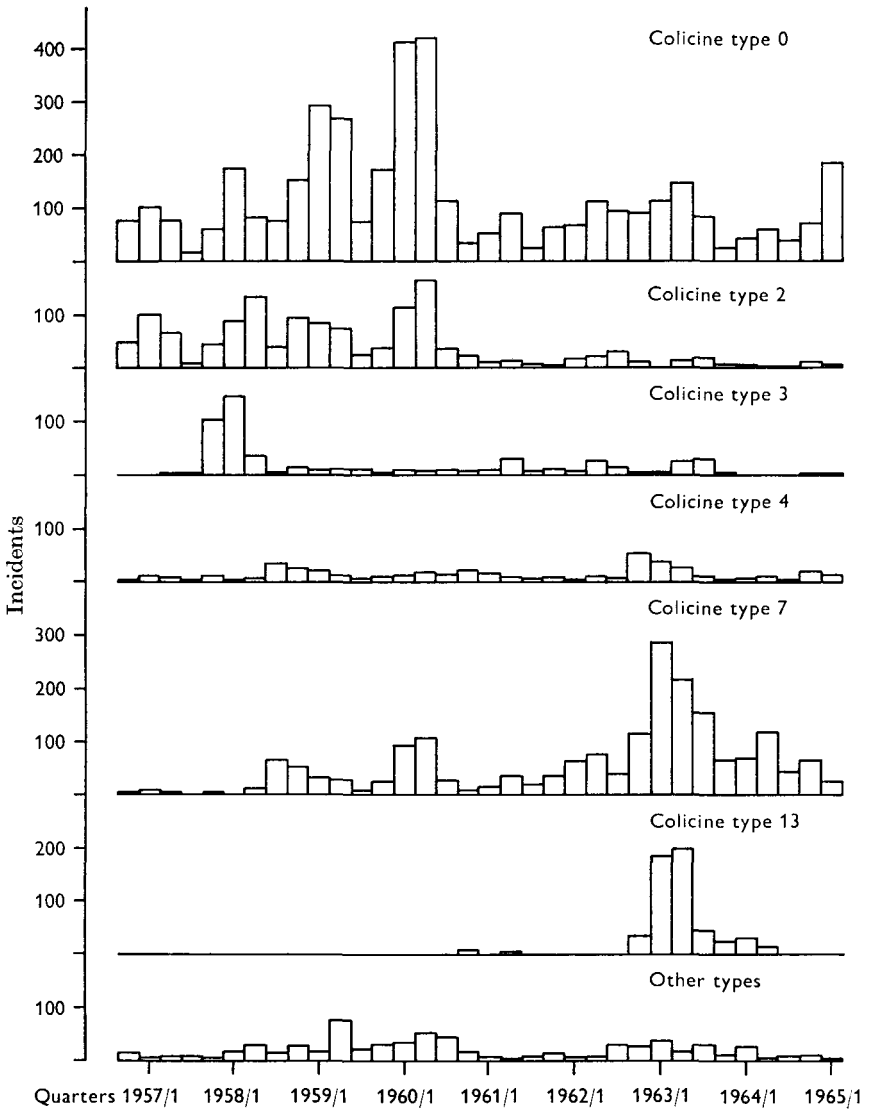

Fig. 2. The quarterly distribution of colicine types of *Sh. sonnei*, 1956–65.

that type 0 is therefore the better name. Nearly half our strains, 3997 out of 9419, produced no colicines; five colicine types, types 2, 3, 4, 7 and 13, were responsible for 4760 incidents. Other colicine types caused 662 incidents, 7 % of the total.

It will be seen from Fig. 2 that three of the six commonly observed colicine types, types 0, 2 and 4, were present in the area and causing infections throughout the

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observation period, but that the other three common types were absent, or virtually so, at the start of the period, gave rise to outbreaks of epidemic proportions and then declined. This sequence is seen most clearly with colicine type 13. No strains of this type were found during the first 4 years, six strains were isolated in West Ham during the 4th quarter of 1960 and a single strain from central London during 1961. Late in 1962, 18 months after the last previous isolation, an epidemic due to this type was observed and by the middle of 1964 a total of 560 incidents due to this type had been recorded; no strains of this type were isolated after June 1964.

The first strains of colicine type 13 that were isolated in 1962 all had the same pattern of antibiotic resistance. They were all resistant to sulphonamides but sensitive to streptomycin and the tetracyclines. A single strain sensitive to sulphonamides was isolated in the last week of 1962 and early in 1963 strains with different patterns of antibiotic resistance were isolated from scattered incidents. Details are given in Table 1.

Table 1. *Number of incidents due to* Shigella sonnei *colicine type* 13

		Antibiotic resistance pattern				
Sulphonamide		S	R	R	R	R
Streptomycin		S	S	R	S	R
Tetracycline		S	S	S	R	R
Year	Quarter					
1962	4	1	36	0	0	0
1963	1	1	175	2	5	0
	2	4	146	1	10	38
	3	4	45	2	13	2
	4	0	4	0	12	9
1964	1	0	1	1	9	23
	2	0	0	0	2	14
	3	0	0	0	0	0

It will be seen that the original epidemic strain had virtually died out, except for five scattered incidents, within 12 months of its original introduction and the epidemic was continued by tetracycline resistant strains that might or might not be sensitive to streptomycin. These in their turn disappeared. The epidemic was largely confined to a group of four contiguous boroughs in North East London. Only fifteen of the 560 incidents occurred outside this area and these did not spread locally.

Altogether strains of this type of *Sh. sonnei* showing five different resistance patterns were encountered. During the first 6 years observation this colicine type was introduced into the area on two occasions; it seems unlikely that introductions of this type with five different resistance patterns should occur over a period of 6 months and that by chance these introductions should all be into that area of North East London where type 13 was already established. It is much more likely that the antibiotic resistance pattern of this organism changed after a single introduction late in 1962.

A rather similar sequence of events can be traced with colicine type 7 though the process has proceeded more slowly and the final elimination of the type had not occurred by March 1965. Details of the antibiotic resistance patterns of all the strains of this type are given in Table 2.

Table 2. *Number of incidents due to* Shigella sonnei *colicine type* 7

		Antibiotic resistance pattern							
Sulphonamide		S	S	S	S	R	R	R	R
Streptomycin		R	R	S	S	S	R	S	R
Tetracycline		R	S	R	S	S	S	R	R
Year	Quarter								
1956 to 1958	4 to 1	.	.	.	1	4	.	.	.
	2	.	.	.	.	10	.	.	.
	3	.	.	.	.	64	.	.	.
	4	.	.	.	.	50	1	.	.
1959	1	.	.	.	2	25	1	3	.
	2	.	.	.	5	22	1	2	.
	3	.	.	.	.	5	1	1	.
	4	.	.	.	5	8	12	.	.
1960	1	.	.	2	42	39	9	.	.
	2	1	2	1	62	33	3	2	.
	3	.	.	.	19	6	1	.	.
	4	.	.	.	5	2	.	.	.
1961	1	.	.	.	8	4	4	.	.
	2	.	.	.	6	30	.	1	.
	3	.	.	.	3	10	1	5	.
	4	.	.	.	.	34	.	.	.
1962	1	.	.	.	1	59	1	4	.
	2	.	.	.	3	69	.	3	2
	3	.	.	.	3	35	.	1	.
	4	.	.	1	25	82	1	4	1
1963	1	.	.	.	23	235	8	14	6
	2	.	1	1	11	161	28	12	4
	3	.	.	1	6	129	9	4	3
	4	.	.	1	4	29	13	12	3
1964	1	.	.	.	3	25	6	26	8
	2	.	.	.	3	26	54	31	4
	3	.	.	.	.	8	20	14	3
	4	.	.	.	.	10	4	47	4
1965	1	.	.	.	.	6	1	17	2

The first five strains of this type were isolated over a period of 18 months from five separate boroughs. In the second quarter of 1958 a sulphonamide resistant strain appeared in Islington—the first type 7 in this borough—and spread at first locally and later over the whole area. At the beginning of the epidemic in 1958 the strains of type 7 all had the same pattern of resistance but later a wide variety of resistance patterns was observed. Strains with the original resistance pattern nearly disappeared in 1959 and in 1960 and were uncommon towards the end of

the period of observations. Table 2 can perhaps best be interpreted as showing a series of overlapping epidemics caused by organisms with different resistance patterns and it seems clear that changes in these resistance patterns occurred from time to time.

Table 3. *Number of incidents due to* Shigella sonnei *colicine type* 3

		Antibiotic resistance pattern					
Sulphonamide		S	R	R	R	R	
Streptomycin		S	S	R	S	R	
Tetracycline		S	S	S	R	R	
Year	Quarter	.	.	.	.	.	
1956	4	.	.	.	.	.	
to		3	.	.	.	.	
1957	3	.	.	.	.	.	
	4	2	105	.	.	.	
1958	1	.	144	.	.	.	
	2	1	34	.	.	.	
	3	.	2	.	.	.	
	4	1	10	.	.	.	
1959	1–4	3	20	.	1	.	
1960	1–4	3	27	.	.	.	
1961	1–4	9	45	.	.	1	35 incidents in Kensington
1962	1–4	.	15	.	29	0	22 incidents in Camberwell
1963	1–4	.	48	3	1	2	47 incidents in Croydon
1964	1–4	1	.	.	.	.	
1965	1	0	0	0	0	1	

Table 4. *Number of incidents due to* Shigella sonnei *colicine type* 3A

		Antibiotic resistance pattern		
Sulphonamide		S	R	R
Tetracycline		S	S	R
Year	Quarter			
1957	3	.	1	.
	4	.	1	.
1958	1	.	6	.
	2	1	9	2
	3	2	4	1
	4	0	0	0

A single incident occurred in 1962.

The sequence of events following the introduction of colicine type 3 into the area was rather different and is shown in Table 3.

Five incidents due to sulphonamide sensitive strains were recorded during 1957, all of which occurred in the borough of Islington where the epidemic due to a

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sulphonamide resistant strain started in the last quarter of 1957. This strain spread into the neighbouring borough of Stoke Newington but was only found elsewhere in very small numbers. The rapid and extensive change of antibiotic resistance pattern observed with types 7 and 13 was not found with this type and apart from localized outbreaks in 1961, 1962 and 1963 of twenty to fifty incidents in single boroughs it has remained an uncommon type.

A similar sequence of events can be seen with some of the less common colicine types. The single example of colicine type 3A must suffice, of which details are given in Table 4. After the end of 1958 a single isolation of type 3A was made in 1962 and two isolations in 1963. All three strains were resistant to sulphonamides but sensitive to streptomycin and tetracycline.

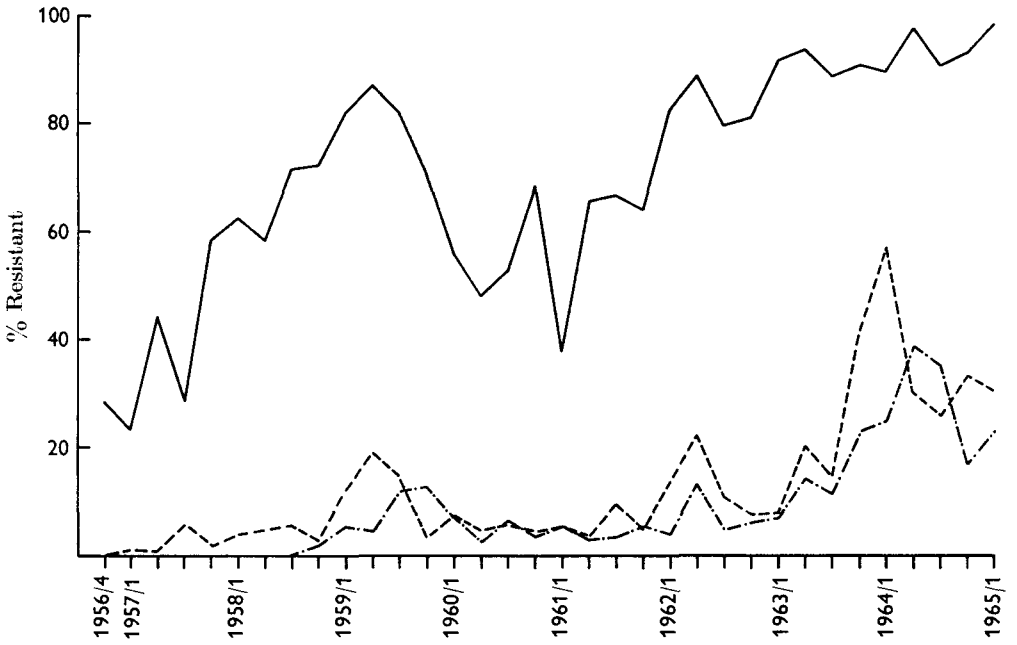

Fig. 3. Changes in sulphonamide and antibiotic resistance of *Sh. sonnei*, 1956–65. ——, Sulphonamide; - - -, tetracycline; — - — -, streptomycin.

It is of interest to see how the overall pattern of antibiotic resistance of *Sh. sonnei* has altered over the years. Details are given in figure 3.

It will be seen that, although the general tendency has been for *Sh. sonnei* to become more resistant to antibiotics this has not been an uninterrupted process. These fluctuations in resistance were related to the resistance patterns of the strain epidemic at any one time and it is clear comparing Fig. 1 with Fig. 3 that increased frequency of resistant strains was not related, except occasionally by chance, to an increased incidence of infection.

During the early part of this study, it seemed that strains of *Sh. sonnei* resistant to streptomycin or tetracyclines or to both drugs were causing for the most part

single incidents and spreading in the community only to a very limited extent, whereas some at least of the strains sensitive to these antibiotics spread widely in the same area. If this were so, the overall percentage of resistant strains would give an underestimate of the frequency with which these resistant strains arose in the community.

It is possible to obtain an estimate of the frequency with which antibiotic resistant strains arose in the community as follows; the number of colicine types recorded for any one borough in any one quarter (borough/quarter) varied between 0 and 9. Each occurrence of antibiotic resistant strains of different colicine type in any one borough/quarter might represent an organism 'newly' resistant whether it gave rise to one or to many incidents. The strains of *Sh. sonnei* from one borough/quarter might fall into 6 colicine types and there might be antibiotic resistant strains from 2 of these colicine types. In another borough/quarter there might be three colicine types one of which had antibiotic resistant representatives. Adding together the figures derived from the individual borough/quarters, the number of colicine types which had resistant representatives would represent the total of 'new' resistant strains, and the frequency of their occurrence can be compared with the frequency of antibiotic resistant strains in the overall totals. This has been done in Table 5. Since the frequency of antibiotic resistant strains has varied, the $8\frac{1}{2}$-year observation period has been divided into four intervals of approximately 2 years and the analysis confined to the fifteen boroughs from which large numbers of specimens have been regularly examined.

Table 5. *Comparison of the frequency of antibiotic resistant strains* (*a*) *of different colicine type in borough/quarters and* (*b*) *overall*

Period	No. of boroughs/ quarters	No. of colicine types	Percentage of colicine types with representatives resistant to			Total incidents	Percentage incidents due to strains resistant to		
			S	T	S and T		S	T	S and T
1956/4–1958/4	129	312	1·0	9·3	0	1888	0·4	3·1	0
1959/1–1960/4	120	424	18·7	18·0	2·4	2942	5·6	8·5	0·4
1961/1–1962/4	120	288	13·2	20·6	4·9	1328	6·2	10·2	1·6
1963/1–1965/1	131	349	34·7	46·5	18·0	2504	16·0	22·0	7·9

Note. Ten borough/quarters not examined. Doubly resistant strains have not been included under resistance to a single antibiotic. S = streptomycin; T = tetracycline.

It will be seen that the proportion of colicine types with antibiotic resistant strains in the borough/quarters was greater, by a factor of two- or three-fold, than the overall proportion of antibiotic resistant strains isolated at the same time. This method of estimating the frequency with which new resistant strains arose is clearly liable to errors due to the persistence of resistant strains in a borough from one quarter to the next and to the spread of a resistant strain over borough boundaries. There is evidence that both these occurrences have happened occasionally and these errors will make the figures in Table 5 for 'new' resistant strains an overestimate. On the other hand, no allowance has been made for the possibility

that a resistant strain of one colicine type might arise on more than one occasion in one borough/quarter; certainly, during the last 2 years when resistant strains have been fairly common, this must have occurred and will compensate to some extent for the other errors. It seems fair to conclude that, in general, strains of *Sh. sonnei* resistant to streptomycin and terramycin did not spread as widely in the general population as did sensitive strains. The fact that localized epidemics due to resistant strains occurred from time to time did not invalidate the general conclusion.

Factors responsible for colicine production can be transferred between members of the Enterobacteriaceae in the same way that resistance factors are transferred and it is not possible to believe that the colicine type of a strain of *Sh. sonnei* remains absolutely constant as it spreads through the community. Gillies (1964) has isolated strains of two colicine types from single individuals and observed a lack of uniformity of colicine type in a small proportion of household and institutional outbreaks which he attributed to mixed infections.

We have investigated 130 outbreaks of Sonne dysentery in day nurseries from which more than one strain of *Sh. sonnei* was examined in detail. All the strains of *Sh. sonnei* in 104 of these outbreaks proved to be identical in colicine type and resistance pattern. In ten outbreaks, strains of the same colicine type but different resistance pattern were observed, in eleven, strains of different colicine type but identical resistance pattern and in five, strains which differed both in colicine type and resistance pattern. Colicine type appeared just as likely to alter as antibiotic resistance.

It was possible to explain some of these discrepancies on the basis of multiple sources of infection but this became more difficult when, as has happened on several occasions, strains of *Sh. sonnei* of different colicine type but all possessing an unusual resistance pattern or other biochemical property were isolated from a day nursery. Similar observations have been made in day schools.

Table 6. *Comparison between the number of incidents and the number of different colicine types in a borough/quarter*

No. of incidents per borough/quarter	No. of borough/quarters	Mean no. of colicine types
0	37	
1–5	164	1·8
6–10	86	2·7
11–20	96	3·2
21–50	78	4·1
51+	39	5·3

Note. Ten borough/quarters not examined.

The number of different colicine types isolated from an area increased as the incidence of Sonne dysentery increased. Taking the borough/quarter as the unit of time and place and confining the analysis to the fifteen major boroughs, it will be seen from Table 6 that the mean number of colicine types detected in a borough/quarter increased as the number of incidents rose.

When large numbers of incidents occurred in a borough/quarter their distribution over the colicine types was not uniform. Usually most of the incidents were caused by one or two colicine types, the other types causing only a few incidents. Since epidemics of Sonne dysentery were often confined to a single borough or group of contiguous boroughs it is difficult to account for these few incidents, due to unexpected colicine types, except on the basis of change from the epidemic type.

Different colicine types appeared to behave differently in the population. Type 0 was present throughout the period under review in all boroughs and often gave rise to epidemics; strains with a particular resistance pattern might be present only for a limited time in a borough but the type as a whole persisted. On the other hand, strains of *Sh. sonnei* of colicine types 1A, 3, 3A, 4 and 13 produced local epidemics lasting 6–15 months in a borough, being virtually absent from that area before and after the epidemic. Intermediate between these two extremes was the behaviour of colicine types 2 and 7. The former, particularly during the early part of our period, tended to give rise to successive annual epidemics in some areas but only to single isolated epidemics in others. Type 7 when first introduced gave rise to local epidemics of finite duration but later caused epidemics going on over several years.

These impressions, that colicine types behaved differently, can be examined mathematically by determining the mean number of incidents per borough/quarter due to each colicine type of *Sh. sonnei*. The figures for the means were obtained by adding together the total number of incidents due to each colicine type and dividing by the number of borough/quarters in which that particular type occurred. Details are given in Table 7 which is confined to the fifteen major boroughs and has been subdivided into 4 periods of approximately 2 years.

Table 7. *Mean number of incidents per borough/quarter due to different colicine types*

	Colicine type								
Period	0	2	3	4	6	7	13	All other types	Total all types
1956/4–1958/4	7·0	6·7	15·7	2·9	2·0	6·1	.	1·8	5·4
	(102)	(82)	(19)	(32)	(27)	(16)	.	(33)	(311)
1959/1–1960/4	15·3	6·3	1·5	2·3	1·7	4·5	6·0	3·9	7·0
	(110)	(82)	(25)	(42)	(36)	(61)	(1)	(58)	(415)
1961/1–1962/4	6·5	2·7	4·9	2·9	1·7	6·0	10·6	1·6	4·6
	(85)	(36)	(19)	(31)	(29)	(65)	(3)	(22)	(290)
1963/1–1965/1	6·8	3·1	6·2	2·9	2·1	9·7	17·6	2·5	5·7
	(102)	(20)	(9)	(36)	(33)	(95)	(29)	(23)	(347)
Total	9·1	5·6	6·8	2·7	1·9	7·1	16·6	2·8	6·3
	(399)	(220)	(72)	(141)	(125)	(237)	(33)	(136)	(1363)

Figures in parentheses indicate the number of borough/quarters from which the relevant colicine type was isolated.

The mean number of incidents per borough/quarter due to a particular colicine type must give a measure of the ability of that particular type to spread in the population and cause overt infection. The figures could be vitiated by irregular

sampling of the population but the long observation period and the number of Local Authorities would seen to eliminate major error on that score.

It is impossible to avoid the conclusion that some strains of *Sh. sonnei*, e.g. types 0 and 7, were better able to spread in the population than other types, such as types 2, 4 and 6; there is also evidence to suggest that the ability of a colicine type to spread might vary with time and was not necessarily constant.

A similar analysis can be carried out to compare antibiotic resistant strains with sensitive strains of the same colicine type. This has been done in Table 8 for types 0 and 7—the only types for which sufficient resistant strains were available.

Table 8. *Mean number of incidents per borough/quarter due to sensitive and resistant strains of types* 0 *and* 7

		Colicine type 0				Colicine type 7			
	Streptomycin	S	R	S	R	S	R	S	R
	Tetracycline	S	S	R	R	S	S	R	R
Period (year and quarter)	1959/1–1960/4	13·0	2·1	4·6	1·0	4·4	1·7	1·2	1·0
		(109)	(31)	(44)	(4)	(56)	(16)	(8)	(1)
	1961/1–1962/4	5·7	2·7	1·8	1·3	5·8	1·4	1·5	2·0
		(77)	(15)	(27)	(8)	(62)	(5)	(11)	(1)
	1963/1–1965/1	5·5	1·5	2·4	3·1	5·4	4·3	3·1	1·8
		(88)	(30)	(42)	(20)	(74)	(30)	(49)	(18)
	Total	8·5	2·0	3·1	2·5	6·4	3·2	2·7	1·8
		(274)	(76)	(113)	(32)	(192)	(51)	(68)	(20)

Figures in parentheses represent the number of borough/quarters in which the appropriate strain appeared.

Table 9. *Drug resistance of colicine type* 6

	All strains except type 6				Strains of type 6			
Period (year and quarter)	Total strains	Sulphon-amide	Strepto-mycin	Tetra-cycline	Total strains	Sulphon-amide	Strepto-mycin	Tetra-cycline
1956/4–1958/4	2033	1158	7	66	58	7	0	0
		(57)	(0·3)	(3)		(12)		
1959/1–1960/4	3069	2025	181	273	67	12	1	4
		(66)	(6)	(9)		(18)	(1·5)	(6)
1961/1–1962/4	1406	1084	89	151	54	11	1	1
		(77)	(6)	(11)		(20)	(2)	(2)
1963/1–1965/1	2664	2497	448	594	68	31	(4	18
		(97)	(17)	(22)		(47)	(6)	(26)

Figures in parentheses are percentages.

Insufficient observations on resistant strains were available during the first $2\frac{1}{4}$ years but thereafter it seems clear that antibiotic resistant strains, on average, gave rise to fewer incidents in those borough/quarters in which they occurred than did sensitive strains.

The behaviour of colicine type 6 has been quite different from that of other colicine types; it has been isolated in small numbers from the whole area through-

out the whole of the observation period, yet the largest number of incidents due to this type in any one quarter has been 21. With one possible exception, it has never given rise to a local epidemic. It appears to be common in continental Europe (Abbott & Graham, 1961) and it has proved to be the type most commonly isolated from patients infected abroad. The sensitivity pattern of strains of colicine type 6 has differed from that of other types in that they were usually sensitive to sulphonamides and very few strains, until 1963, were resistant to streptomycin and the tetracyclines. Details are given in Table 9 from which it will be seen that strains of this colicine type are able to acquire resistance but have been slower to do so than the other types.

DISCUSSION

The most striking feature of this survey has been the appearance of new colicine types and new patterns of antibiotic resistance among strains of *Sh. sonnei* both in the area as a whole and in the individual boroughs. While, for example, it might be possible to account for the appearance of colicine type 13 in late 1962 on the basis of importation from outside, it is not possible on this basis to account for the fact that strains of this type with at least five different resistance patterns were isolated from north-east London during the subsequent 6 months. The fact that the number of colicine types isolated from an area increased as the frequency of Sonne dysentery increased in that area (Table 6) and that the incidents were not evenly distributed over the colicine types can most easily be explained on the basis that the more widespread the *Shigella* the greater will be the variety of strains of *E. coli* with which it comes in contact and the greater the opportunity for the acquisition of new colicine factors. This observation is in line with that of Gillies (1964) who found different colicine types in eight out of 480 households but in fifteen out of sixty-seven institutional infections. In the latter, a strain of *Sh. sonnei* would experience contact with a wider range of coliforms.

The changes in antibiotic resistance and colicine type observed over the $8\frac{1}{2}$ years can be best regarded as a result of the interaction and transfer of characters between *Sh. sonnei* and other intestinal organisms. The change from sensitive to resistant has been most marked with regard to sulphonamides, yet even here the change has not been constantly progressive. Davies (1954) selected strains from the area we examined in the same manner as ours and found 61% of strains resistant to sulphonamide with a marked difference between different areas. This contrasts with our finding that 24% of strains in the first quarter of 1957 were resistant, and shows that the fluctuations in resistance which can be seen in Fig. 2 certainly started before 1954. The proportion of strains of *Sh. sonnei* isolated from the population that are resistant or sensitive to a particular antibiotic merely reflects the resistance pattern of the current epidemic strain.

It seems inevitable that the proportion of strains resistant to streptomycin and tetracycline will increase. Antibiotic therapy—for dysentery or for some completely different condition—may allow a resistant strain of any member of the Enterobacteriaceae present in the gut in small numbers to become the dominant organism, to be passed to others and transfer its resistance to other organisms. At the same

time the human population is being continually infected with antibiotic resistant organisms derived from farm animals. Salmonellas derived from slaughter houses appear in the human population (McDonagh & Smith, 1958; Report, 1965) and the much more numerous *E. coli* derived from animals must do the same.

The epidemiology of Sonne dysentery in London as revealed by colicine typing has been characterized by local outbreaks, sometimes spreading into neighbouring areas, rather than generalized epidemics. A total of 286 incidents were recorded during the winter of 1957/8 due to type 3; all but 8 of these occurred in the adjacent boroughs of Islington, Stoke Newington and Shoreditch. During the epidemic due to type 13 which lasted for 2 years and was responsible for 560 incidents, only fifteen of these incidents occurred outside a group of contiguous boroughs in north-east London. Both of these episodes can be regarded as large local epidemics. Colicine type 7 gave rise to a generalized epidemic over the whole area during the winter of 1962/3 but when this strain first occurred during the summer of 1958, it was largely confined to a single area.

We have observed, on several occasions, the more or less simultaneous isolation of an unusual colicine type from a few incidents in two or more widely separated areas. In view of the failure of *Sh. sonnei* to spread widely from established local epidemics, it is difficult to account for this on the basis of a common source of infection. An alternative hypothesis would assume that the unusual colicine type originated *de novo* in several places at once. The widespread dissemination of a strain of *E. coli* with the appropriate colicine factors, e.g. in raw or cooked food, might allow local strains of *Sh. sonnei* to take on new colicine characters in several areas at the same time.

There is evidence that different strains of *Sh. sonnei* vary in their ability to spread widely through the population. These differences are shown in Table 7 for colicine type and in Tables 5 and 8 for strains resistant to streptomycin and tetracycline. These tables suggest that strains of colicine types 0, 7 and 13, sensitive to streptomycin and tetracycline, are more likely to spread widely than other strains. The power to spread widely did not seem to be possessed by all strains with these characters and was certainly not exclusive to them since sharp local episodes were caused, at one time or another, by strains of colicine type 1A, 2, 3, and 4.

Another phenomenon that requires explanation is the disappearance from the human population of strains of *Sh. sonnei* characterized by colicine type and antibiotic resistance. A small proportion of resistant organisms in a culture can be shown in the laboratory to have lost their resistance and to have reverted to sensitivity (Datta, 1962) but this seems unlikely to account for the disappearance of resistant strains from the human population. Strains of *Sh. sonnei* resistant to streptomycin and tetracycline often spread less widely than sensitive strains and might be expected to die out during the summer months, when Sonne dysentery is least common, simply because they failed to infect new individuals at the rate at which convalescent carriers ceased excreting. Such an explanation does not account for the disappearance of a strain such as the original epidemic type 13 sensitive to streptomycin and tetracycline. This strain, originally capable of spreading widely, spread through a population of about 1,000,000, gave rise to numerous incidents

and disappeared some 15 months after its original introduction. Many other similar, though less spectacular, episodes could be quoted.

It is tempting to ascribe to epidemic strains of *Sh. sonnei* a special 'ability to spread' that is not possessed by the majority of other strains and which is not related to any character at present detectable in the laboratory. This 'ability to spread' might merely be a power to outgrow the other organisms in the gut and to produce a higher concentration of *Sh. sonnei* in the faeces, but many other possibilities exist. It would be necessary to assume that this 'ability to spread' was an unstable character in order to account for the decline and disappearance of epidemic strains but some transferred characters may also be unstable. Certainly, some characters—antibiotic resistance and colicine production—can be transferred to *Sh. sonnei* in the laboratory and the evidence produced here suggests very strongly that this also happens in the human population. There is no reason why other characters which cannot yet be distinguished in the laboratory should not also be transferred to *Sh. sonnei*. Such an hypothesis which would ascribe part, at least, of the rise and fall of epidemics of Sonne dysentery to changes in the organism runs somewhat contrary to the teaching of classical epidemiology. The latter has not been particularly successful at explaining the spread of this infection so it is worth considering an alternative.

SUMMARY

The colicine type and antibiotic resistance have been determined on strains of *Sh. sonnei* derived from 9419 incidents of Sonne dysentery in London between October 1956 and March 1965.

The most striking observation has been the appearance of strains with patterns of colicine production and antibiotic resistance new to the area. These changes are best regarded as a result of the interaction and transfer of characters between *Sh. sonnei* and other intestinal organisms.

The general tendency has been for strains of *Sh. sonnei* to become increasingly resistant to antibiotics but this has not been an uninterrupted process. The proportion of drug-resistant strains at any one time depended on the properties of the current epidemic strain.

Spread of Sonne dysentery was essentially local, but some strains of *Sh. sonnei* were found to spread much more widely than others. Most, but not all, of the strains resistant to streptomycin and tetracycline possessed only limited powers of spreading.

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