CROSS INFECTION IN DIPHTHERIA WARDS

By V. GLASS and H. D. WRIGHT

Department of Bacteriology, University of Liverpool

It has been shown by Okell & Elliott (1936) and also by Gunn & Griffith (1928) and Allison & Brown (1937) that cross infection is a relatively common occurrence in wards where cases of infection with haemolytic streptococci are being treated. The recognition of this fact has been rendered possible by the use of serological methods as described by Griffith (1934). That something of the same sort may occur in diphtheria wards was suggested by the observation of Anderson and his colleagues (Anderson *et al.* 1933) that change of the type of bacillus could be detected in a proportion of cases but not in wards to which cases of one type only were admitted. Similar findings are recorded by Robinson (1934). Our attention was first directed to the problem when certain of our clinical colleagues sought an explanation of variation in the results of virulence tests on strains of diphtheria bacilli isolated at different times from convalescent patients. We soon satisfied ourselves that in one and the same case at different times virulent and non-virulent strains might succeed one another or even alternate. This was in complete disagreement with the findings of Graham Smith (Nuttall & Graham Smith, 1908) who showed that while cultures from convalescent cases of diphtheria were not consistently positive the strains which were isolated remained as at the beginning, virulent or non-virulent, throughout convalescence until they finally disappeared. In the hope of clearing up this apparent discrepancy we obtained through the courtesy of Dr Hodgson, Superintendent of Fazakerley Fever Hospitals, a series of swabs from the nose and throat of cases of diphtheria both on admission and at intervals thereafter as determined by clinical requirements. In all cases where diphtheria bacilli were found the type was determined and virulence tests were done with all strains of the *mitis* type. No virulence tests were made on organisms of the *gravis* or "intermediate" types as a considerable number of previous tests had shown that non-virulent organisms of these types are so rare in Liverpool as to be negligible. For typing we used the medium described by Glass (1937) the classification based on colonial appearances being confirmed by fermentation tests as suggested by Anderson *et al.* (1931) and by consideration of growth characteristics in liquid media.

Frequency of occurrence of cross infection

The information obtained refers to 246 cases examined during the winter of 1935–36. No case was considered which did not remain under observation for at least a month. The general results are recorded in Table I.

Table I. *Alterations in type of diphtheria bacillus in convalescent cases*

Period of observation	Total	Findings constant	Findings variable		
			– on admission +later	Type changed	Total
More than 2 months	63	20	10	33	43
More than 1 month, not more than 2 months	132	95	12	25	37
One month only	51	41	6	4	10
	246	156	28	62	90

Out of 246 cases there were therefore 156 or 63·4% in which the findings remained constant throughout the period of investigation, but in 90 or 36·6% some change was observed. In 62 cases (25·2%) the original type present was replaced or became accompanied by a new one; in 28 cases (11·4%), admitted on notification as diphtheria, no diphtheria bacilli could be found in the nose or throat on their entry into hospital but they were present at a later date.

It will also be seen that the proportion of cases with variable findings as regards diphtheria bacilli increases with the length of stay in hospital. Of those under observation for 1 month only, 10 out of 51 (19·6%) showed some change; in the group examined for periods between 1 and 2 months changes occurred in 37 out of 132 (28%) and of those studied for longer periods in 43 out of 63 (68·3%). There is thus some evidence to suggest that it is in the later stages of the convalescent period that alterations in type or acquisition of bacilli occur.

NATURE OF CHANGES OBSERVED

The changes were quite irregular in kind and gave no sort of indication of any steadily progressive process in a definite direction. They may be summarized as follows:

Mitis virulent to *mitis* non-virulent	3 cases
Mitis to *gravis*	4 ,,
Mitis to "intermediate"	8 ,,
Mitis to *gravis* +"intermediate"	1 ,,
Mitis followed by multiple changes	5 ,,
"Intermediate" to *mitis*	13 ,,
"Intermediate" to *gravis*	8 ,,
"Intermediate" followed by multiple changes	5 ,,
Gravis to *mitis*	6 ,,
Gravis to "intermediate"	9 ,,

In the 28 cases which yielded no diphtheria bacilli on admission but acquired them during their stay in hospital the new acquisitions were also varied. Seven were of the *mitis* type, 6 "intermediate" and 4 *gravis* while in 11 cases more than one new type was found. In one of these cases a non-virulent *mitis* strain was succeeded by an "intermediate" which in turn gave place to a virulent *mitis* and this again to a *gravis* strain.

A few detailed observations may be of interest.

S. 769 Original type G			S. 827 Original Neg.			S. 647 Original type M			C. 1502 Original Neg.		
6 days later		Neg.	18 days later		Neg.	8 days later		Neg.	4 days later		M
7	,,	G	4	,,	M	7	,,	Neg.	3	,,	M
7	,,	Neg.	6	,,	I	7	,,	G	18	,,	I
10	,,	Neg.	10	,,	Neg.	14	,,	G + (M)	35	,,	G
5	,,	Neg.	2	,,	Neg.	7	,,	G + (M)	30	,,	G
27	,,	I	3	,,	M	7	,,	Neg.	13	,,	G
10	,,	I	4	,,	G	7	,,	M	21	,,	I
1	,,	Neg.	6	,,	G	15	,,	M			
7	,,	I	11	,,	Neg.	10	,,	M + (M)			
20	,,	I	5	,,	Neg.	16	,,	M + (M)			
8	,,	I				5	,,	Neg.			
14	,,	Neg.				6	,,	M.			
2	,,	Neg.				1	,,	Neg.			
1	,,	Neg.				2	,,	Neg.			
						4	,,	M			
						7	,,	M			
						2	,,	Neg.			

G = *Gravis*. I = "Intermediate." M = *Mitis* virulent. (M) = *Mitis* non-virulent.

The change from an initial infecting type to one of a different kind might be an expression of bacterial variation but we do not think this is the case. Murray (1935), Mair (1936) and others have certainly suggested that change of type may frequently be induced *in vitro* but the balance of evidence (Robinson, 1934; Cooper *et al.* 1936) seems to us to indicate that the types are quite stable. Cases which acquire the diphtheria bacillus for the first time during their stay in hospital must be regarded as hospital infections. We see no reason to place changes of type occurring in hospital in any other category. Our observations upon groups of cases occurring in families or under circumstances of close contact between cases seem to us to lend support to the idea of the epidemiological independence of the different types. Altogether we have observed the types in 98 such groups comprising 217 cases. In 94 of the groups with 208 cases the types were the same in all members of the group, *mitis* in 27, *gravis* in 34 and "intermediate" in 33. In the remaining 4 groups, containing 9 cases, the infecting types were different within the group. In one group one patient had a *mitis* infection and the other a *gravis*, in another the types were *mitis* and "intermediate". The interval between the admissions to hospital was 28 days in the first and 31 in the second group and the infections may well have had independent sources. In the third group, one case was a *mitis* infection and the other a *gravis*—interval 7 days—and in the fourth a mother and one child were infected with an "intermediate" strain and a second child with a *mitis*. We think, with Anderson *et al.* (1933) that the evidence speaks strongly for the independent existence of the different types and that the changes occurring in hospital result from cross infection.

CLINICAL SIGNIFICANCE OF THE CHANGES OF TYPE

In spite of the quite unexpected frequency of change of type we could not ascertain that such changes had any effect on the clinical course of the disease in this series. In another series 4 cases admitted without diphtheria bacilli in the throat became infected in hospital and developed clinical manifestations and one patient died. While therefore the risk of harm to the patient is surprisingly small, yet it does exist.

ADMINISTRATIVE SIGNIFICANCE OF THE CHANGES OF TYPES

The frequency of cross infection in the investigation described above was to us so surprising that we wished to see if it occurred in other hospitals. In the course of another investigation in three quite distinct hospitals for infectious diseases in Liverpool we have been able to satisfy ourselves that cross infection does occur and probably not infrequently. Through the courtesy of the Resident Medical Officers concerned we were able to ascertain the facts tabulated in Table II in regard to the patients in the wards on a certain day.

Table II. *Causes of prolonged hospitalization in diphtheria*

Hospital	Cases of diphtheria	Cases in hospital more than 2 months	Reasons for prolonged stay	
			Clinical	Persistent positive swabs
I	53	20	5	15
II	123	33	6	27
III	105	47	13	34
	281	100	24	76

It will be seen that of the 281 cases in hospital on this particular day 100 had been there for longer than 2 months. Of these only 24 were detained for clinical reasons, 76 because of the persistence of diphtheria bacilli in the nose or throat. In 51 out of these 76 we have information as to the type of organism present both at the beginning of their illness and at a later stage. In 8 cases (15·7%) there had been no change; in 2 (3·9%) the original type was found in addition to a new one; in 41 (80·4%) the type had changed. There were 14 cases which had been in hospital more than $3\frac{1}{2}$ months. In two cases this long hospitalization was due to clinical developments. The remaining 12 were detained solely for bacteriological reasons and in 11 out of the 12 the type of organism present was different from the one which caused the original infection. In several cases more than one change had occurred. One case was admitted as a carrier of what proved to be a non-virulent strain of the *mitis* type. After 160 days it was discharged, having finally rid itself of the original organisms and two virulent strains of *gravis* and "intermediate" type which it acquired during its stay. It appears then that a prolonged carrier condition in hospital is not always or even commonly due to persistence of the original infection but usually to reinfection with a fresh strain, an idea which has already been

suggested by Harries (London County Council, 1935). It is evident that this problem is one of administrative importance and that cross infection must be a significant contributor to the cost of diphtheria hospitalization.

There is also another aspect of this question which has attracted our attention. A case of diphtheria which occurs in a house within 4–6 weeks after the return of a patient treated in hospital for diphtheria is regarded as a "return case" and attributed to infection from the convalescent. We wished to know whether the type of organism was the same in the "return case" as in the original. In four instances we have found that this was so. In five others, however, the "return case" was infected with a different type. In one of these the interval between the return of the first patient and infection of the second was about 5 weeks and the infection might well have been acquired from some other source. In three others the "return" cases developed within a week of the first patient's return home from hospital. The last of the series has seemed to suggest an explanation of this apparent discrepancy. The first patient in the family, aged 2 years, was infected with a *mitis* type, had a mild attack of diphtheria and soon rid herself of the infection as evidenced by three negative cultures from nose and throat. She was discharged on 7. iii. 37. Within a day or two of her return home she developed a discharge from one ear. On 14. iii. 37 a second member of the family developed diphtheria, a third on 8. iv. 37 and a fourth on 22. iv. 37. These three cases were all infected with organisms of the "intermediate" type. We therefore had swabs taken from the first patient and found bacilli of the "intermediate" type in the ear and the nose. It appears probable that having rid herself of the original infection the first patient of the series had become reinfected with an organism of the "intermediate" type which may have caused the otitis and was then distributed among the other members of the family. We have since had experience of two other instances where patients have yielded three consecutive negative cultures, remained in hospital 3 weeks longer and then provided a culture of diphtheria bacilli different from the type originally present. Such occurrences seem to us to provide one feasible explanation of differences in type of infecting organism between original and "return" cases. They suggest that if freedom from diphtheria bacilli is to be demanded before patients are discharged from hospital the examinations should be made as near the time of discharge as possible and if the patient is subsequently detained for any length of time, say more than a week, a further examination should be made.

Discussion

The results of this investigation may be summarized as indicating that cross infection in the diphtheria wards of infectious diseases hospitals is not at all uncommon. To the patient admitted in error to a diphtheria ward it offers certain dangers and this provides an argument for the reception of dubious cases into special observation wards. To the diphtheria patient, however,

reinfection appears to be associated with little or no risk in contradistinction to reinfection with scarlet fever streptococci as indicated by Allison & Brown. But from the point of view of hospital administration cross infection is a matter of considerable importance. In our first investigation 36% of all cases were reinfected during their stay in hospital and if that stay lasted longer than 2 months the percentage rose to about 70. Our second study showed that about one-third of the patients in our diphtheria wards had been there for longer than 2 months and that three-fourths of these were detained solely because diphtheria bacilli were still found in the nose or throat. About 80% of these "carriers" owed their condition and prolonged hospitalization to reinfection. According to our experience the hospital carrier is not usually in that position because of persistence of his original infection but as the result of reinfection to which for some reason he is specially prone or particularly exposed.

It has been suggested that the difficulty might be overcome by hospitalizing the patients in different wards according to the type of infecting organism. We are not satisfied that this would obviate cross infection though it might obscure it. We know of no evidence to indicate that a patient cannot be reinfected with his original type. If he were, there is no means of telling whether the later strain is different from the original, at any rate so far as the "intermediate" and *gravis* types are concerned in Liverpool. Cross infection as suggested by Allison & Brown might occur in a number of ways but we agree with them and with Anderson *et al.* (1933) that it is highly probable that contact with other convalescents is of the greatest importance especially where the convalescents who are usually children play together regardless of the bacterial content of their upper respiratory tracts. If such be the source, and this can only be decided by further work on the subject, it is clear that the solution will be an expensive one, possibly involving the use of cubicle wards, but, although we are unable to calculate it on our present data, the cost of cross infection at the present time is not an inconsiderable one. We have had at least a dozen cases in the last few weeks in which hospitalization for periods of from 120 to 160 days was solely due to this factor, at an average cost of about £50 per patient.

SUMMARY

1. Evidence is adduced to indicate that cross infection occurred in 36·6% of a series of 246 patients in diphtheria wards.

2. In patients who were in hospital longer than 2 months it occurred in 68%.

3. Persistence of diphtheria bacilli in the upper respiratory tract was responsible for prolongation of hospitalization in 76% of cases in a series examined.

4. In 80% of these cases this persistence was a result of cross infection.

5. The administrative importance of cross infection is discussed.

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REFERENCES

ALLISON, V. D. & BROWN, W. A. (1937). *J. Hygiene*, **37**, 152.

ANDERSON, J. S., HAPPOLD, F. C., MCLEOD, J. W. & THOMPSON, J. G. (1931). *J. Path. Bact.* **34**, 667.

ANDERSON, J. S., COOPER, K. E., HAPPOLD, F. C. & MCLEOD, J. W. (1933). *Ibid.* **36**, 169.

COOPER, K. E., HAPPOLD, F. C., MCLEOD, J. W. & WOODCOCK, H. DE C. (1936). *Proc. Roy. Soc. Med.* **29**. Section of Pathology, 5.

GLASS, V. (1937). *J. Path. Bact.* **44**, 235.

GRIFFITH, F. (1934). *J. Hygiene*, **34**, 542.

GUNN, W. & GRIFFITH, F. (1928). *Ibid.* **38**, 250.

LONDON COUNTY COUNCIL (1935). *Annual Report of the Council for* 1934, **4**, Part 1, p. 93.

MAIR, W. (1936). *J. Path. Bact.* **42**, 635.

MURRAY, J. F. (1935). *Brit. J. exp. Path.* **16**, 532.

NUTTALL, G. H. F. & GRAHAM SMITH, G. S. (1908). *The Bacteriology of Diphtheria*, pp. 408–13. Cambridge.

OKELL, C. C. & ELLIOTT, S. D. (1936). *Lancet*, ii, 836.

ROBINSON, D. T. (1934). *J. Path. Bact.* **39**, 551.

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