THE DIPHTHERIAL INFECTION IN SCARLET FEVER.

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THE association of scarlet fever and diphtheria is of considerable interest and there is already a fairly extensive literature on the subject, but more particularly from the point of view of post-scarlatinal diphtheria. The following paper contains some further observations on the association of diphtheria-like bacilli with the acute stage of scarlet fever and on the effect of this association on the patient. The work was carried out at Ruchill Hospital, Glasgow, and the writer is greatly indebted to the Physician-Superintendent, Dr W. M. Elliott, for suggestions and criticism throughout.

Statistics. It is generally known that a small percentage of scarlet fever patients is found after admission to hospital to harbour organisms morphologically indistinguishable from the Klebs-Loeffler bacillus. The percentage varies considerably according to different observers, and according to the situation in which the organisms are found. These situations are the ear, nose and throat. The organisms cultivated from aural discharge (8, 11, 15) have been found to be for the most part non-virulent and it is held (2) that, while diphtheria-like bacilli are very common in the ear complications following scarlet fever, true virulent diphtheria bacilli are rare. The examination of the nose (1, 6, 7, 8, 14) on admission reveals the presence of these organisms in 8·6 per cent. to 12·7 per cent. of all cases of scarlet fever and, while they are in the majority of cases non-virulent, true virulent diphtheria bacilli are much more commonly found in this situation than in the ear.

As regards the throat, the numbers of cases found by other observers (1, 3, 4, 5, 6, 7) to harbour diphtheria-like organisms on admission varies from 1·2 to 5·8 per cent., while if the examination is made at a later date the percentage becomes very much greater (8, 9, 10). At this hospital, careful records of all these cases have been kept for the past ten years, but no systematic observations were made of the ear and nose, nor until the winter of 1914–15 was cultural examination of the throat of all cases of scarlet fever made a routine on admission. From 1910–14 only those cases of scarlet fever whose throats showed the presence of membranous angina, or whose throats were "suspicious" were subjected to cultural examination, and this is particularly interesting as it allows of a comparison over the two periods, not only as to the prevalence of these cases but as to the question of post-scarlatinal diphtheria as seen in the wards of the hospital. In all cases the swab for cultivation was taken shortly after admission, sown on solidified serum, and examined

after 12 to 24 hours' incubation in smear preparations stained by the London modification of Neisser's method. Cases showing the presence only of Hoffmann's bacillus (and they were numerous) are excluded from this series. During this ten years' period, 14,770 cases of scarlet fever were admitted to the hospital and of these 283 are recorded as harbouring in the throat organisms morphologically indistinguishable from the diphtheria bacillus. Yearly details are given in the following table. The dates correspond with hospital years from June 1 to May 31. The year 1914–15 is transitional in that routine cultivation was then gradually introduced, and the figures are not comparable with the years before or after. It will be seen from the table that there is a considerable yearly variation in the numbers of these cases. As would be expected the figures are very much increased since the introduction of routine examinations, an average for 1915–20 of 2·9 per cent. as against 1·1 per cent. for 1910–14. These yearly variations since 1915 do not follow any very definite line, but on the whole the tendency is upwards. This is probably to be ascribed to the fact that in these years occurs the rise of the decennial diphtheria cycle for the Glasgow district—its lowest point falls in 1915 and it rises to the year 1920. It has been shown (Richards) that the prevalence of post-scarlatinal diphtheria in hospital also varies with that of diphtheria outside.

Table A.

	Year	Scarlet fever admissions	Diphtheria-like bacilli present	Percentage of admissions
No routine cultivation	1910–11	1768	17	0·96
	1911–12	1222	7	0·57
	1912–13	1260	25	1·9
	1913–14	1930	22	1·1
Totals and mean	4 years	6180	71	1·1
Transition year	1914–15	2455	32	1·3
Routine cultivation	1915–16	2422	35	1·4
	1916–17	1181	55	4·6
	1917–18	475	11	2·3
	1918–19	512	23	4·4
	1919–20	1542	56	3·6
Totals and mean	5 years	6132	180	2·9

In Table B the mean monthly admission over these five years of scarlet fever patients harbouring diphtheria bacilli are compared with the mean monthly admission of diphtheria itself. These latter figures are given as the statistics for the monthly local incidence are not available; but as very few cases of diphtheria are treated at home in this area, the admission rate may be taken to correspond very closely to the local prevalence of diphtheria.

Table B (1915–20).

	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May
Mean monthly admissions of diphtheria	29·4	31·4	34·8	46·4	68·0	57·4	57·2	58·2	54·0	54·4	41·7	37·6
Mean monthly percentage of scarlet fever admissions with diphtheria bacilli	2·1	3·8	2·1	4·0	2·6	3·0	4·3	4·0	2·7	1·6	2·3	1·9

As with the yearly prevalence, so the seasonal prevalence does not definitely follow that of diphtheria but there is on the whole a larger number of scarlet fever patients showing diphtheria-like bacilli in the fauces during the months in which the incidence of diphtheria is high than at any other time of the year.

It may be noted in passing that the *sex distribution* of the 283 cases in question showed a slight preponderance of females, 163 to 120 males, which is in accordance with that of diphtheria itself, and with post-scarlatinal diphtheria.

It is also of interest to note that only 17 of the 283 cases gave a history of having had diphtheria prior to admission, and in only five was there a history of contact with a case of diphtheria. In 12 cases the previous history was not recorded.

Clinical Findings.

All the cases were in the acute stage of scarlet fever. The majority showed no clinical evidence of the presence of the diphtheria-like organisms. This is shown in Table C, in which the cases are grouped according to the faucial lesion. Groups 1 to 4 correspond to the usual description of the throat in scarlet fever.

Groups. (1) Congestion; (2) further inflammation, enlarged tonsils covered with sticky mucus; (3) patching of tonsils, *i.e.* presence of a yellow scum either as a continuous pellicle or as separate areas of exudation easily removable as a rule and leaving no bleeding or abrasion on removal (Kerr(12)); (4) ulceration of tonsils, pillars of fauces or palate. To include all the cases three other groups require to be added, namely: (5) fauces congested with presence of membrane of "wash-leather" type; (6) fauces congested only but in addition signs of laryngeal embarrassment; and (7) fauces congested only but in addition membranous rhinitis.

Table C.

Group	1	2	3	4	5	6	7	Totals
1910–14	4	—	24	6	35	2	—	71
1914–15	11	2	8	5	6	—	—	32
1915–20	69	36	41	7	24	2	1	180
Totals	84	38	73	18	65	4	1	283

As has been already stated, before the introduction of routine culturing in 1914–15, only those cases whose throats showed membranous angina, or were "suspicious" from the point of view of diphtheria, were examined bacteriologically, and naturally, as seen in the above table, they fall into Groups 3 to 7. The four exceptions in Group 1 were discovered by their being sent to the hospital as diphtheria, though their condition on admission did not support this diagnosis. In the years 1915–20 the majority of the cases (105 out of 180) fall into Groups 1 and 2, that is to say, the faucial lesion was limited to congestion with enlargement of the tonsils. The presumption is that in these cases scarlet fever and faucial diphtheria are not present simultaneously, but that they are instances of scarlet fever developing in diphtheria carriers. Moreover, the same can be said of all cases in Groups 1 to 4, for in these the lesions are

nothing more than is ordinarily found in scarlet fever, and the proportion of cases with patching or ulceration is not more than normal. Conditions are different in the remaining groups where membrane is present (in the laryngeal cases its presence is inferred). Here, moreover, several points have to be taken into consideration. These cases may be instances of co-existing diphtheria and scarlet fever, of scarlet fever alone with membranous angina, or of true diphtheria with an erythematous eruption. This last possibility is very remote, for though a case of diphtheria may show an erythematous rash it is usually in the form of a diffuse blush not punctate and not with the distribution characteristic of scarlet fever. Further, these cases were treated in the scarlet fever and diphtheria ward without subsequently developing scarlet fever. This they would almost certainly have done had they been cases of true diphtheria alone, for it is well known that diphtheria patients are particularly prone to the infection of scarlet fever.

With regard to the second possibility, membrane formation does occur in scarlet fever of the septic or streptococcic type, and certain of these cases are said to develop subsequently the paralyses found in true diphtheria. However, the membrane is not usually of the definite wash-leather type, does not, as a rule, extend to the larynx, and is accompanied by considerable oedema, ulceration and necrosis. Also, it is but very rarely that such cases develop the diphtheritic palsies. Since in the cases under consideration organisms indistinguishable morphologically from the Klebs-Loeffler bacillus have been shown to be present together with a membranous lesion, and since we know that, not uncommonly, other infectious diseases do occur, simultaneously in the same patient, it would seem reasonable to consider them instances of double infection. When the subsequent histories are taken into account further evidence is found to support this view. Here, too, difficulties arise in attempting to attribute occurrences in the course of scarlet fever to a superadded diphtheria. Apart from the rash in scarlet fever and the membrane in diphtheria, the signs and symptoms are somewhat similar in average cases of these two diseases, such phenomena as pyrexia, albuminuria, adenitis and the slighter cardio-vascular disturbances are common to both. Also the majority of such cases, after the subsidence of the acute stage, pass on to an uninterrupted recovery. This occurred in the 213 cases included in Groups 1 to 4. With three exceptions all ran a comparatively mild course without complications or sequelae. The three exceptions (two in Group 3 and one in Group 4) became septic and died, a case mortality for the combined group of 1·3 per cent. which is well within the average for scarlet fever. This, too, would bear out the contention that these cases were originally diphtheria carriers who had developed scarlet fever. On the other hand Groups 5 to 7 present a striking contrast. The single case in Group 7 gives no further evidence, for though sharply ill and showing considerable toxaemia on admission, it passed on to an uninterrupted recovery. Of the four laryngeal cases (Group 6) two had septic scarlet fever but recovered, one case died of sudden cardiac failure.

The severity of the subsequent course is best seen in the 65 cases in Group 5. The majority showed a considerable degree of toxaemia, while adenitis, albuminuria and rhinorrhoea were very frequent, only 11 cases making an uninterrupted recovery. In the remaining cases of the group, 17 developed sepsis, five of them dying; five showed various diphtheria paralyses as well as sepsis, two dying of sudden heart failure; while ten showed diphtheritic palsies but no sepsis, of whom nine died of cardiac failure—a total of 16 deaths, giving a case mortality of 24 per cent. for the Group 5 alone. The high death-rate and the frequency of sepsis are in keeping with the anginose form of scarlet fever, but the occurrence of the diphtheritic palsies and sudden cardiac failure in so many points definitely to the co-existence of true diphtheria with the scarlet fever.

Broadly speaking, then, these cases may be divided into two main groups, namely, those with scarlet fever and "cultural" diphtheria and those with scarlet fever and co-existing true faucial diphtheria, the added infection in the former being of little significance clinically, but being of grave import in the latter group. From the administrative point of view, those with membranous angina are always treated as cases of double infection and isolated from the scarlet fever wards, but with regard to the cultural cases considerable difference of opinion exists. When discovered they are not always isolated, and more often no routine examination is carried out for their discovery. It is said that in the great majority of cases the organism present is non-virulent, that the results of cultures on admission are fallacious, and that the labour involved in a routine examination would not be repaid by any corresponding diminution of outbreaks of post-scarlatinal diphtheria. From this point of view a series of 14 cases in Group 1 has been examined bacteriologically, as it is in this group that there is least of all evidence to suspect the presence of virulent diphtheria bacilli.

Bacteriology.

The primary cultures were taken from patients shortly after admission, the medium used being solidified serum. Isolation of pure strains of diphtheria-like organisms from the primary culture was accomplished in the usual way by repeated examination and sub-culturing. The 14 strains under consideration were all morphologically indistinguishable from the Klebs-Loeffler bacillus, and showed a similar want of uniformity in size arrangement and staining reactions. Details are given below in Table D. The fermentative reactions and pathogenicity bear no relation to the morphological character of the bacillus.

The fermentative reactions were carried out in Hiss's serum water medium with 1 per cent. of the sugars added. Cultures were examined 48 hours after inoculation and thereafter every day for ten days. Incubation was then stopped and the cultures re-examined for contamination. Although the action on glucose is generally taken as being sufficient to distinguish the true diphtheria bacillus, the opportunity was taken to observe the action on the other sugars as described by Graham Smith (2) and the results given in Table D very closely

agree with those recorded by him. All the 14 strains produced acid in glucose, galactose, laevulose and maltose, while none had any action on mannite. Acid was produced in dextrine and glycerine by 12 strains, in lactose by 11, and in saccharose by four. With many, coagulation of the medium also occurred specially with the more readily fermentable sugars. According to Kolmer and Moshage (13) it is dependent on the amount of the organic acid present, and it will be seen that in this series coagulation did not occur with anything less than a markedly acid reaction. From their cultural reactions, the 14 strains are seen to be true diphtheria bacilli.

Table D.

Morphology	Glucose	Galactose	Laevulose	Maltose	Dextrine	Glycerine	Lactose	Mannite	Saccharose	
1. Short bacilli, rather uniformly staining	A C	A C	A C	X	0	0	0	0	A C	Non-pathogenic
2. Short bacilli, streptococcal form	A C	A C	A C	A C	0	0	A C	0	A C	Non-pathogenic
3. Medium length, polar staining	A C	A	A	A	X	X	X	0	0	Non-pathogenic
4. Medium length, polar staining	A C	A C	A C	A C	X	X	X	0	A C	Pathogenic
5. Medium length, polar staining	A C	A C	A C	A	X	N	0	0	0	Pathogenic
6. Medium length, irregularly beaded	A C	A C	A C	A C	A	X	X	0	0	Non-pathogenic
7. Medium length, irregularly beaded	A C	A C	A C	A	X	A C	A C	0	A C	Pathogenic
8. Medium length, irregularly beaded	A C	A	A C	A C	A C	A	0	0	0	Non-pathogenic
9. Medium length, granular, large and dark	A C	A	A C	X	A C	X	0	0	0	Non-pathogenic
10. Long bacilli, polar staining	A C	A	A C	A	X	X	X	0	0	Pathogenic
11. Long bacilli, polar staining and beading	A C	A C	A C	A C	X	A C	0	0	0	Non-pathogenic
12. Long bacilli, polar staining and beading	A C	A	A C	X	X	X	N	0	0	Pathogenic
13. Long bacilli, irregularly beaded	A C	A	A C	A C	A C	X	X	0	0	Non-pathogenic
14. Long bacilli, barred type	A C	A C	A C	A C	A	A	A	0	0	Non-pathogenic

N = slightly acid or neutral. X = acid. A = markedly acid. C = coagulation. 0 = no effect.

Pathogenicity was tested by the subcutaneous inoculation of guinea-pigs with suspensions in saline of 24 hours' serum cultures (13). The animals were kept under observation for ten days, and post-mortem examinations made. By this method, five strains were found to be fully virulent, the guinea-pigs dying within 48 hours with the lesions characteristic of experimental diphtheria, namely, local necrosis and congestion of the internal organs, particularly intense in the suprarenals. Eight strains had no observable effect on inoculation, while one produced only a slight and transient local oedema without general symptoms.

The only other comparable series of which the writer is aware, is that

recorded by Pugh. Five strains from similar cases were tested and found non-virulent, though all produced acid in glucose, and the general impression is that the organisms in the great majority of such cases are non-virulent. However, the present series would tend to show that true virulent diphtheria bacilli are much more numerous than is supposed, and this is specially important with regard to post-scarlatinal diphtheria. Also important from this point of view is the period of persistence of such organisms. Cumpston finds that they tend to persist for long periods and the following observation also bears this out. In 43 cases of scarlet fever with cultural diphtheria, the organisms persisted beyond the fourth week of stay in hospital in 13 instances as follows:

To	5th week	1	
„	6 „ „	4	1 being virulent
„	7 „ „	2	
„	8 „ „	1	Virulent
„	10 „ „	2	
„	11 „ „	1	
Beyond	12 „ „	2	1 virulent. Patients then dismissed.

Post-Scarlatinal Diphtheria.

The routine cultivation commenced in 1914–15 was introduced with a view to further reducing the incidence of post-scarlatinal diphtheria. However, owing to the excessive number of scarlet fever patients under treatment during the years 1914–16, the isolation of all cases found on admission to harbour diphtheria bacilli could not be carried out until 1916–17. It will be seen on reference to Table E that since complete isolation commenced there has been a decline in the prevalence of post-scarlatinal diphtheria. It is noteworthy that during these years the prevalence of diphtheria in the district supplying the hospital was on the increase, and it has been shown that ordinarily the prevalence of post-scarlatinal diphtheria in hospital varies with that of diphtheria outside.

Table E.

	1910–11	11–12	12–13	13–14	14–15	15–16	16–17	17–18	18–19	19–20
Cases of scarlet fever completed	1860	1300	1205	1881	2473	2446	1335	516	504	1330
Cases of post-scarlatinal diphtheria with: Faucial lesions	8	17	4	3	6	32	11	3	1	2
Cases of post-scarlatinal diphtheria with: Cultural diphtheria only	1	20	4	7	7	84	9	3	—	2
Total	9	37	8	10	13	116	20	6	1	4
Percentage of cases completed	·49	2·84	·66	·53	·52	4·07	1·49	1·16	·19	·30

One other point of view remains to be noted. It has been stated(2) that in the great majority of instances in which these two diseases occur in the same patient diphtheria follows the attack of scarlet fever. This, however, has not been the case here. During the same ten years 216 of 6754 cases of diphtheria completed, developed post-diphtheric scarlatina—an incidence of over 3 per cent. as compared with 1·3 per cent. for post-scarlatinal diphtheria.

CONCLUSIONS.

From consideration of the above evidence the following conclusions may be drawn:

(1) The prevalence of diphtheria-like bacilli in the fauces of scarlet fever patients on admission to hospital does not definitely follow that of diphtheria outside either in seasonal or yearly prevalence.

(2) The majority of such patients show no clinical evidence of the added infection. It is believed that they are instances of scarlet fever developing in diphtheria carriers, and the presence of the organism does not affect the prognosis. However, cases which present such clinical evidence as a membranous angina are to be considered as instances of true double infection and in them the prognosis is bad.

(3) Bacteriological examination of a series of cases belonging to the former group reveals the presence of true virulent diphtheria bacilli in about 36 per cent., and these organisms may persist in a virulent state for a considerable period.

(4) Routine bacteriological examination to find these cases and their subsequent isolation materially reduces the incidence of post-scarlatinal diphtheria.

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