TREATMENT OF DIPHTHERIA CARRIERS AND "POSITIVE"

THROATS WITH KLEBS-LOFFLER BACILLUS VACCINE.

by

F. G. FOSTER, M.B., Ch.B.

Thesis for the Degree of M.D.

March 1922.
The bacillus of Diphtheria in a virulent form may be found in the throats of healthy persons.

These may suffer no inconvenience from its presence yet are capable of infecting others who have less resistance to the organism. Such carriers may have never suffered and may never suffer from Diphtheria. A. Reith Fraser and A.G.B. Duncan published a paper in the Lancet towards the end of 1920 on the treatment of Diphtheria Carriers with Detoxicated Klebs-Loffler Vaccine (1), and, in a leading article in the same issue, a commentator on their paper wrote as follows:

"The authors define a Carrier as one who harbours virulent pathogenic organisms, and is capable of infecting others, though not himself exhibiting any of the clinical signs of the disease. They distinguish between the so-called "positive throats" - which are practically cases of delayed resolution, where the bacilli persist for more than three months - and the true Carrier, where the bacilli remain for long periods with unabated virulence in spite of energetic methods of disinfection."

On the subject of convalescent carriers C.B. Ker (2) states: "It" (i.e. their number) "is large enough, however/
however, to make the management and treatment of carriers a most important question. How are we to free the patient, or how long is he to be kept in hospital? As to the first of these questions it must be admitted that treatment generally appears inefficacious. The carrier is usually a child with large and ragged tonsils and the bacilli probably lie in the crypts and are not easily reached by whatever antiseptic is employed." He goes on to say that he has found gargles to be of little service in clearing up such cases. Caustics, e.g. Nitrate of Silver and sprays of living organisms of Staphylococci aurei or Lactic Acid bacilli have been tried with indifferent success. Injections of antistreptococcal serum are claimed to have got rid of the bacilli in some cases where the throat harboured a large number of other pathogenic organisms in addition to the Klebs-Löffler bacillus.

J.L. Brownlie (3) published a paper in March 1920 describing his results on the treatment of "positive" throats with a Stock Klebs-Löffler bacillus vaccine. He treated 50 consecutive "positive" throats by this method and found that 37 cleared up within a week and 7 within a fortnight. Of the remaining 6 all but one gave negative cultures within
30 days of the commencement of the treatment.

His dosages varied between 10 and 20 million organisms and he stated that "pyrexia and local pain or stiffness were quite exceptional". He did not mention whether any of the cases were "nasal", - by which I mean patients with intermittent or persistent nasal discharge containing the Klebs-Löffler bacillus.

In September 1920, I took over charge of the Diphtheria Ward in the Leicester Isolation Hospital, and amongst my patients was one who had been in hospital for over seven months and from whose trachea the Klebs-Löffler bacillus could still be cultivated.

He had been tracheotomised over six months previously after being intubated on many occasions and was at the time I saw him, unable to dispense with a tracheotomy tube.

Cultures from the mucus from the tracheotomy opening proved persistently positive.

Local treatment not being possible in his case, it occurred to me to try and attack the bacillus through the blood-stream and hence I put him on a course of injections of Detoxicated Klebs-Löffler bacillus vaccine.

The success I attained in his case encouraged me to pursue this form of treatment whenever a suitable/
suitable case presented itself.

At this time I could find no literature on treatment by such methods as the article by Reith Fraser and Duncan was not published until Nov. 13th 1920, and I had not seen the article by Brownlie on treatment by Stock Vaccines.

I resolved to try treatment with Detoxicated Vaccine on all cases where the nose or throat gave a positive culture after four weeks' stay in hospital, as well as on all carriers that came my way. By carriers I accepted the definition quoted above, and of such I encountered only four cases during my stay in Leicester: the remainder of the cases cannot even be classed as "positive throats" (i.e. giving positive swabs after three months), although it is possible that some might have become such - or at least one liked to think so - if treatment had not been instituted. The cases of diphtheria during the time I was at Leicester Isolation Hospital (Sept. 1920 - Nov. 1921) were for the most part not of a severe type, and I did not find many patients whose throats gave positive cultures after a month's stay in hospital. Our custom was not to discharge a patient until two successive negative swabs had been obtained.
Any means, therefore, of causing the speedy disappearance of the bacillus from the throat or nose is welcome, as it shortens the isolation of the patient, and thus both saves money to the Corporation and gratifies the parents anxious for the return of their child.

The first series of cases I treated with a Detoxicated Klebs-Löffler bacillus vaccine which was obtained from the Genatosan Company. It was prepared by Thomson’s method and 1 cc. contained 100,000 million bacilli.

Then I treated a series of cases with a Stock Klebs-Löffler bacillus vaccine which was much cheaper than the detoxicated form.

This was procured from Burroughs, Wellcome & Co. and 1 cc. contained 50 million bacilli.

The following are the cases which I treated with Detoxicated Vaccine.

CASE I. F.B., a boy aged 2½ years, admitted 26th Feb. 1920 in my predecessor’s time. On admission he had a croupy cough, obstructive breathing with marked recession. 10,000 units of antitoxin were injected. He was intubated and required re-intubation on about 20 occasions/
occasions during the week following his admission, as he kept coughing out the tube and was never able to do without it.

Tracheotomy was performed on 3rd March, and, after a sharp attack of broncho-pneumonia, he made a good recovery.

He could not breathe, however, per vias naturalis if the tracheotomy tube was blocked, and he was seen by a throat specialist who diagnosed damage to the vocal cords and consequent obstruction to the air-entry. The specialist said that he would admit him to his ward in the Leicester Royal Infirmary whenever his throat gave a negative swab.

When he came under my charge in Sept. 1920, a swab taken from the mucus in the tracheotomy opening still gave a positive culture, and previous swabs taken at intervals during the preceding six months had usually proved positive.

He had therefore developed into a Carrier. Accordingly in October I determined to try him on a course of Detoxicated Klebs-Loffler bacillus vaccine.

As I mentioned before, no literature on treatment of such cases with this vaccine had been published at that time, and this accounts for the comparatively small dosages with which I started. I gave the following injections subcutaneously.
7.10.20  5,000 million Detoxicated K.-L. bacilli (.05 cc.)
14.10.20  10,000 "  "  " (.1 cc.)
19.10.20  20,000 "  "  " (.2 cc.)

A swab taken on the 16th showed Hofmann bacilli and three successive swabs taken after the 20th at intervals of three days proved negative. Several swabs taken subsequently were also negative.

CASE 2.  L.H., boy aged 7, admitted 22.10.20 with membrane on both tonsils and thick greenish discharge in nasopharynx.
6000 units Antitoxin were injected intramuscularly.
15.11.20  Throat swab culture positive.
17.11.20  "  "  "  "
18.11.20  5000 million Detoxicated K.-L. bacilli (.05 cc.) injected.
21.11.20  Throat swab culture negative
24.11.20  "  "  "  "
26.11.20  "  "  "  "

CASE 3.  J.R., kitchen-maid in the hospital, aged 22, admitted 20.11.20 with patches on both tonsils.
6000 units antitoxin intramuscularly.
21.11.20./
CASE 4. E.B., woman, aged 36, admitted

16.11.20 with small patch on R. tonsil.

8000 units antitoxin intramuscularly.

13.12.20 Throat swab positive.

10,000 million Detoxicated K.-L. bacilli (.1 cc.) injected.

15.12.20. Throat swab negative - Hofmann.

18.12.20 " " "

21.12.20 " " "

CASE 5. P.C., girl, 4½ years of age, admitted

16.10.20 with scarlet fever.

22.10.20 Complained of earache.

23.10.20 Discharge from nose.

23.11.20/
23.11.20 - 28.11.20. Pyrexia varying between 99° and 100.8°F.

27.11.20. Culture from nasal discharge showed Klebs-Löffler bacilli.

Tonsils and faucial clear. Transferred to Mixed-Infections Ward. 6000 units antitoxin injected. Up to Dec. 31st she was treated by my colleague, but on Jan. 1st, 1921, she came under my charge, and it was at this time that the article by Fraser and Duncan first came under my notice.


20.12.20. Nose discharging more freely.


22.12.20. 5000 million Detoxicated bacilli (.05 cc.) injected.

Supply of Vaccine finished.


11.1.21. 25,000 million Detoxicated bacilli (.25 cc.) injected.


14.1.21. 50,000 million Detoxicated bacilli (.5 cc. injected)


17.1.21. 100,000 million Detoxicated bacilli (1 cc. injected)

19.1.21/
22.1.21. " " "
25.1.21. " " "

CASE 6. F.W., boy 23 months of age.
21.12.20. Admitted with small patches on both tonsils, marked laryngeal stridor, dyspnoea and recession.
2000 units antitoxin injected before admission.
8000 " " " after admission.
Intubated and tube removed two days later.
25.1.21. Throat swab positive.
31.1.21. " " "
1.2.21. 50,000 million Detoxicated bacilli (0.5 cc.) injected.
3.2.21. Throat swab.- Involution forms.
4.2.21. 100,000 million Detoxicated bacilli (1 cc.) injected.
5.2.21. Throat swab negative.
8.2.21. " " "
11.2.21. " " "

CASE 7./
CASE 7. N.C., girl, aged 4.

4.1.21. Admitted with membrane on both tonsils and profuse nasal discharge. Very croupy with recession.

Intubated 10,000 units antitoxin.

5.1.21. 6000 units antitoxin injected.

7.1.21 - 20.1.21. Extubated on three occasions and on each required re-intubation.

21.1.21. Tracheotomy performed.

Child unable to dispense with tube afterwards and was a case similar to Case 1.

8.2.21. Throat swab positive.

9.2.21. 50,000 million Detoxicated bacilli (.5 cc.) injected.

11.2.21. Throat swab positive.

12.2.21. 100,000 million Detoxicated bacilli (1 cc.) injected.

15.2.21. Throat swab positive.

16.2.21. 150,000 million Detoxicated bacilli (1.5 cc.) injected.

18.2.21. Throat swab positive.

19.2.21. 200,000 million Detoxicated bacilli (2 cc.) injected.


22.2.21. 250,000 million Detoxicated bacilli (2.5 cc.) injected.
Swabs on Feb. 24th, 27th, 29th, March 30th, April 2nd and 5th were negative and she was transferred to Leicester Royal Infirmary for operative treatment.

CASE 9. G.F., female aged 24: a domestic servant, formerly a maid in a Fever Hospital, was discovered to be a carrier and to have infected a child in the house in which she was working.

29.4.21. Admitted on a positive swab: faucial slightly inflamed.
30.4.21. 50,000 million Detoxicated bacilli (.5 cc.) injected.
2.5.21. Throat swab negative.
5.5.21. " " "
8.5.21. " " "
11.5.21. " " "
13.5.21. " " "


30.4.21. Admitted with nasal discharge which gave a positive culture. Both nostrils full of crusts of dried discharge. Tonsils normal. Was suffering no discomfort and was running about at home. Probably a carrier.
50,000 million Detoxicated bacilli (.5 cc.) injected and nose swabbed with Eusol.

2.5.21. Nasal swab negative.

4.5.21. Nasal and throat swabs negative.

7.5.21. " " " " Discharge dried up.

29.5.21. " " " " No discharge.


16.6.21. Admitted with patches of membrane on both tonsils.

8000 units antitoxin injected.

14.7.21. Throat swab positive.

17.7.21. " " "

19.7.21. 100,000 million Detoxicated bacilli (1 cc.) injected.

21.7.21. Throat swab positive.

22.7.21. 200,000 million Detoxicated bacilli (2 cc.) injected.


25.7.21. 500,000 million Detoxicated bacilli (5 cc.) injected.

Evening Temp. 100.2°F.


27.7.21. Throat swab negative.

Three successive negative swabs at later dates.

The/
The next three cases were treated by my successor after I had left the hospital, and I am indebted to him for particulars.


          8000 units antitoxin injected.
28.10.21. Throat swab positive.
31.10.21. " " "
4.11.21. " " "
5.11.21. 50,000 million Detoxicated bacilli (.5 cc.) injected.
8.11.21. Throat swab positive.
          100,000 million Detoxicated bacilli (1 cc.) injected.
11.11.21. Throat swab negative.
          Three successive negative swabs at later dates.

CASE 13. R.P., boy aged 11.

27.12.21. Admitted with membrane over whole of Right tonsil.
          6000 units Antitoxin injected.
23.1.22. Throat swab positive.
30.1.22. " " "


100,000 million Detoxicated bacilli (1 cc.) injected.

2.2.22. Throat swab positive.
4.2.22. 150,000 million bacilli (1.5 cc.) injected.
6.2.22. Throat swab positive.
7.2.22. 200,000 million bacilli (2 cc.) injected.

Four successive negative swabs.


18.1.22. Admitted with deposit on both tonsils.
         6000 units Antitoxin injected.
20.1.22. Deposit now become a membrane.
         6000 units Antitoxin injected.
18.2.22. Throat swab positive.
         100,000 million Detoxicated bacilli (1 cc.) injected.

Four successive negative swabs.

The following cases were injected with Stock Klebs-Löffler Vaccine.

CASE 15. D.M., boy aged 5 years.

1.4.21. Admitted suffering from Scarlet Fever.
15.4.21. Thick yellowish discharge from nostrils:
         crusts in nose.
11.5.21./

4000 units antitoxin injected.

30.5.21. Nasal swab positive but practically no discharge from nose.

12.5 million Stock Klebs-Löffler bacillus Vaccine (.25 cc.) injected.

Four successive negative swabs.


7.4.21. Admitted with medium-sized patches of membrane on both tonsils.

6000 units Antitoxin injected.

20.4.21. Slight palatal paralysis.

8.5.21. Throat swab positive.

11.5.21. " " "

15.5.21. " " "

20.5.21. 12.5 millions Stock bacilli (.25 cc.) injected.

21.5.21. Throat swab negative.

Three successive negative swabs at later dates.

CASE 17./
CASE 17. J.W., man aged 21.

21.4.21. Admitted. Tonsils raw and inflamed as if membranes had separated. 4000 units Antitoxin injected.

18.5.21. Throat swab positive.

20.5.21. 12.5 million Stock bacilli (.25 cc.) injected. Evening Temp. 99°F.

22.5.21. Throat swab positive.

23.5.21. 25 million Stock bacilli (.5 cc.) injected. Evening Temp. 99.2°F.

25.5.21. Throat swab - Transitional and Hofmann.

26.5.21. 50 million bacilli (1 cc.) injected. Four successive negative swabs.


4.5.21. Admitted with membrane on tonsils and uvula. 8000 units antitoxin injected.

29.5.21. Throat swab positive.

1.6.21. " " "

3.6.21. " " "

12.5 million Stock bacilli (.25 cc.) injected. Evening Temp. 100°F.

5.6.21. Throat swab positive. Evening Temp. 99.2°F.
6.6.21. 25 million bacilli (.5 cc.) injected.  
          Evening Temp. 100.2°F.
8.6.21. Throat swab negative. Temperature normal.  
        Three later negative swabs.

CASE 19. M.H., girl aged 3 years.

10.5.21. Admitted with thick membrane on tonsils  
         and uvula: croupy respirations and dis¬  
         charge from nose.  
         8000 units Antitoxin injected at 11 a.m.  
         4000 " " " at 10 p.m.
4.6.21. Throat swab positive.
8.6.21. " " "
10.6.21. 12.5 million Stock Klebs-Loffler bacilli  
         (25 cc.) injected.
12.6.21. Throat swab positive.
13.6.21. 25 million bacilli (.5 cc. injected).  
         Stock of Vaccine finished: awaiting  
         fresh supply.
15.6.21. Throat swab positive.
19.6.21. Throat swab positive.
21.6.21. 50 million bacilli (1 cc.) injected.
23.6.21./
23.6.21. Throat swab - transitional.
24.6.21. 75 million bacilli (1.5 cc.) injected.
27.6.21. 100 million bacilli (2 cc.) injected.
29.6.21. Throat swab negative.
2.7.21. " " 

Four negative swabs at later dates.
This child developed small septic spots on face 
and neck on 15.6.21, which did not clear up until a 
fortnight later.

CASE 20. Eva G., girl, aged 2 years.

16.5.21. Admitted on a positive swab. Throat 
inflamed but no membrane.
2000 units Antitoxin.
12.6.21. Throat swab positive.
14.6.21. Throat swab positive.
12.5 million Stock bacilli (.25 cc.) 
injected.
16.6.21. Throat swab positive.
17.6.21. 25 million bacilli (.5 cc.) injected.
20.6.21. 50 million bacilli (1 cc.) injected.
22.6.21. Throat swab negative.

Six other successive negative swabs. This case, 
also, developed septic spots on face and hands 
similar to last case.

24.6.21. Re-admitted. Had been discharged six weeks previously after she had given one negative swab. A nasal discharge, which had cleared up in hospital, had recommenced 2 weeks after her discharge, and she had infected one brother and two sisters with Diphtheria.


27.6.21. 25.5 million Stock bacilli (.5 cc.) injected.

29.6.21. Nasal swab positive.

30.6.21. 50 million bacilli (1 cc.) injected.

1.7.21. Nasal swab positive.

3.7.21. 75 million bacilli (1.5 cc.) injected.

5.7.21. Nasal swab negative.

Three later nose and throat swabs proved negative.

CASE 22. V.F., girl, aged 7.

10.6.21. Admitted on a positive swab, with excoriation of Right nostril and slight nasal discharge. Throat clear. Child running about at home and suffering no discomfort.

11.6.21./
12.6.21. 12.5 million Stock bacilli (.25 cc.) injected.

Five later swabs proved negative.

CASE 23. This, the last case, and the only one which failed to clear up, was treated with detoxicated vaccine.

M.L., girl aged 5 years, treated in the Isolation Hospital for Diphtheria from June 25th to Sept. 18th 1920, was re-admitted on Oct. 2nd., with a nasal discharge which gave a positive culture.

The child did not appear to be suffering.

7.10.20. 5000 million Detoxicated bacilli (.05 cc.) injected.
9.10.20. Nasal swab negative.
10.10.20. 10,000 million bacilli injected (.1 cc.)
12.10.20. Nasal swab - Involution forms.
Discharge much less.
13.10.20. 20,000 million bacilli (.2 cc.) injected.
15.10.20. Nasal swab negative.
18.10.20. Nasal swab negative and discharge dried up.

Discharged as there was great congestion in the Ward owing to number of new patients.

8.4.21./
8.4.21. Re-admitted with muco-purulent discharge from nose which gave a positive culture.
9.4.21. 100,000 million Detoxicated bacilli (1 cc.) injected.
11.4.21. Nasal swab positive.
12.4.21. 150,000 million bacilli (1.5 cc.) injected.
15.4.21. 200,000 million bacilli (2 cc.) injected.
17.4.21. Nasal swab positive.
18.4.21. 300,000 million bacilli (3 cc.) injected.
20.4.21. Nasal swab positive.
21.4.21. 600,000 million bacilli (6 cc.) injected.
23.4.21. Nasal swab positive.

As the child had very large tonsils and adenoids I thought that removal of these might clear up her condition.

23.6.20. Tonsils and adenoids removed at Royal Infirmary.
11.7.21. Nasal swab positive.

I tried her again on a course of detoxicated Klebs-Loffler vaccine and gave her four injections commencing with 100,000 million bacilli (1 cc.) and finishing with 750,000 million (7.5 cc.) She gave occasional negative swabs but the majority were positive and she was discharged on 4.8.21 with a still persistent nasal discharge which gave a positive/
positive culture. Beyond local stiffness and swelling she never exhibited any general reaction to the Vaccine in spite of the largeness of the final dose.

I am of opinion that the bacillus in this case was of an avirulent type. She had several brothers and sisters, and lived in a congested area of Leicester, yet there was never any case of diphtheria traceable to infection from her. We were unable to verify this by injecting the organism into a guinea-pig, as we had no licence to perform operations on animals.

In only one case was there any general reaction to the Detoxicated vaccine, and here there was slight malaise accompanied by an evening temperature of 100.2°F. In several cases there was local pain and stiffness at the sites of infection, but this was never very lasting or troublesome to the patient.

With the Stock Vaccine several patients exhibited general reactions in the form of malaise and pyrexia. Two children developed spots on face, neck and hands after their injections.

Local pain and stiffness were no more marked with this form of vaccine than with the detoxicated.
All the injections were given subcutaneously in the morning. Swabs were taken in the evening of the day following.

The bacteriology in every case, except in Cases 12, 13 and 14 and part of Case 6, was done by myself.

The Culture Medium used was Solidified Blood Serum as supplied by Baird and Tatlock and the methods of staining employed were Neisser's and Pugh's.

SUMMARY.

Twenty-three cases were treated with Klebs-Löffler Vaccine, of which fifteen received the detoxicated, and eight the Stock Vaccine.

One case failed to clear up and I am unable to give any explanation for the failure.
The following tables summarise the results of the other twenty-two cases.

### Cleared up.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Within 1 week</th>
<th>Within 2 weeks</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detoxicated</td>
<td>11</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Stock</td>
<td>7</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

### Cleared up.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>After 1 injection</th>
<th>After 2 injections</th>
<th>After 3 injections</th>
<th>After more than 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detoxicated</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Stock</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

Of the 23 cases, four were true carriers, and of these three cleared up; the fourth was the only one of the 23 cases which failed to clear up. There is little to choose between the Detoxicated and the Stock Vaccine. Each gave equally good results. The former has the disadvantage of being much more expensive than the Stock and this becomes more noticeable as much larger quantities of it require to be given.

With the Stock Vaccine I found more cases giving general reactions, but Brownlie, who treated 50 cases, although he did not employ as large dosages as I did, stated/
stated that "pyrexia and local pain or stiffness were quite exceptional".

The Stock Vaccine has the advantage of being much cheaper.

The largest initial dose which I gave of the detoxicated variety was 100,000 million bacilli (1 cc.) and the largest final dose was 750,000 million (7.5 cc.) With the Stock Vaccine I always commenced with 12.5 million (.25 cc.) and the largest final dose I gave was 100 million bacilli (2 cc.)

I had hoped to pursue vaccine treatment at the Isolation Hospital of Birkenhead, where I am now resident, but, during the four months I have been here, the Medical Officer, who had promised to allow me to treat any carriers or "positive throats", has not had any cases answering to this description.

I would suggest that the following line of treatment be adopted in such cases:-

1. An initial injection of 50,000 million detoxicated bacilli to a child under 2 years, and of 100,000 million to any case over that age. The injection to be given in the morning.
2. Swab taken on the evening of the day succeeding the day of infection.

3. If positive, an injection of double the dose to be given on the next morning but one.

4. A swab to be taken as before and, if positive, dosage to be increased by 100,000 million bacilli.

5. If the Stock Vaccine be employed the initial injection to be 12.5 million to a child under two, and 25 million to patients over that age.

6. If swab be positive, the second injection to be double the dosage of the first.

7. If further injections be necessary, doses to be increased by 25 million bacilli.

I believe that in practically all cases a negative swab will be obtained by the time that 500,000 million (5 cc.) detoxicated or 100 million Stock (4 cc.) Klebs-Loeffler bacilli have been injected.

REFERENCES/
REFERENCES.

