THESIS PRESENTED FOR M.D. GLASGOW UNIVERSITY.

by

Campbell Kay Stevenson, M.B., Ch.B., Glasgow 1907.

Temporary Lieutenant R.A.M.C.

War Hospital,
D U N D E E,
April, 1916.

Title:-

OBSERVATIONS on VARIOUS METHODS of TREATING PERSISTENT DIPHTHERIA.

The following observations on Diphtheria were made while Resident Assistant Physician at the City of Glasgow Fever Hospitals (Belvidere and Ruchill), and at the London Metropolitan Fever Hospitals (South Western and North Eastern), 1909/13.

This work does not propose to deal with the treatment of Diphtheria in its acute stages. Attention is confined to personal observations on the treatment of persistent Diphtheria Bacilli in patients convalescent from Diphtheria and to the treatment of the true carrier case, that is the case where virulent Diphtheria Bacilli are found in the throat or nose of a host who has not had any known attack of Diphtheria.

There is great diversity of opinion as to the length of time convalescent diphtheria patients should be kept in hospital. Some local authorities allow patients out soon after the clinical signs disappear. Others send them out after four weeks' residence, but most authorities do not now recognise any arbitrary limit and only allow cases to be dismissed when they have a succession of negative swabs from the throat and nose. If then the diphtheria bacilli are long in disappearing, this means a prolonged stay in hospital, extra expense to the ratepayers, as well as being irksome to the patient and patient's friends. Any method of treatment, therefore, which would help to clear up these cases quickly, would be of great benefit.

There is no known reason why diphtheria bacilli should persist in certain cases and not in others.

According to the observations of Meikle (1), the duration of the persistence of bacilli is not appreciably affected by season, sex, age, number of days ill before serum was given, the amount and position of membrane, the amount of antitoxin given, or the date of disappearance of the membrane. These conclusions are generally accepted.

(1) Meikle (XII - 1906) Edin. Med. Journal XX, 510.

The various statistics published (2) show that Diphtheria Bacilli may remain for very long periods in the throat and nose of a convalescent patient, and may retain their full virulence.

Sims Woodhead (3) examined a large number of cases treated in the Metropolitan Board Fever Hospitals and he found the mean period of persistence was fifty one days. This figure is very much higher than that given by other observers. The average period seems to be about thirty one days.

It is in the throat and nose that the bacilli lodge, on the surface and in the crypts of the tonsils, in the fissures of adenoids, the spaces about the turbinates, and the sinuses connected with the nose - the Antrum, the Frontal and Sphenoida

o/ Smooth mucus membrane is not a good harbour for them. They lurk in corners where there is not a sufficient stream of mucous to dislodge them.

Beyer (4) reports that he found diphtheria bacilli in the urine in one case in nineteen of children examined four to fourteen weeks after an attack of diphtheria. This observation has not been confirmed, but if it is correct it will be an additional problem for the public health authorities.

I have gone on four great general lines of attack in treating persistent diphtheria cases.

1. The local application of Antibacterial agents.
2. The removal of lodgment areas where possible (tonsils and adenoids).
3. Active immunization (vaccines).
4. Replacement of diphtheria germ by other organisms antagonistic to it.

---

(2) Nuttal & Smith, Bact. of Diphtheria. page 420.

(3) Sims Woodhead, 1901 Met. Asylum Board Report, page 271.

(4) Beyer, Munch. Med. Wochenschr 1913, LX, No. 5.

The local application of antibacterial agents may be made by:-

1. Gargles.
2. Coarse Sprays.
3. Douches.
4. Atomizers (fine sprays).
5. Painting with pigments.
6. Administration of antiseptic pastilles.
7. Insufflation of powders.
8. Inhalations.

Gargles.

Gargles with various watery solutions, for example, solutions of Pot. Chlor. Boracic Acid, weak Carbolic Acid, Permanganate of Potash were used, but we were early convinced of their inefficacy. In the majority of cases they are of no more use than a simple mouth wash.

In the first place the large majority of persistent cases are in children and it is extremely difficult to teach a child to gargle. Even with adults it is difficult to get them to gargle efficiently. This can easily be proved by getting a number of patients to gargle with a solution of methylene blue or charcoal. It is found that the large majority of them never get the solution beyond the fauces.

Coarse Sprays

Coarse Sprays of many different solutions were tried in a very large number of cases. Practically all the common antiseptics were used but with the exception of silver nitrate solution 5% to 10% no antiseptic seems to be much better than the other. The best type of spray I found out after trying many patterns was the De Vilbiss spray. This spray has a long nozzle which can be used as a tongue depressor and it has a movable piece at the tip so that the fluid can easily be directed in any direction. It is easy to pass the nozzle behind the soft palate and when the end piece is turned up a stream of fluid may be thrown on the post nasal tissues. When using the spray on young children the mouth is best kept open

by/

by means of a small gag and an assistant should control the movements of the child who should be wrapped in a blanket. As I stated the solution I had the most success with was Nitrate of Silver 5% to 10%. In at least twenty persistent cases I found the diphtheria bacilli disappear after a week to fourteen days' treatment with this solution. Spraying I found was not carried out well by nurses, and in most cases I did it at least once a day myself. In the early stages of my fever work I used the spray also for the nose when there were diphtheria bacilli and a profuse nasal discharge present. Spraying of the nose is not recommended, however, as infection may be carried into corners where it has not yet reached, and in some cases it may cause otitis media. It was found in nose cases that the application of a solution of silver nitrate on a swab to the nasal mucous membrane was much more satisfactory.

Douches.

Douches of various solutions were given either by a ball syringe, funnel and tube, or by a glass douche. Douching of the throat by throwing in a large volume of solution is the best method of applying antiseptic solutions to the throats of children under seven. Children should be wrapped up in a blanket with their hands bound in and turned well round on their face. The mouth is opened and kept so by a metal spatula and the contents of the ball discharged into the throat. This should be repeated three or four times. In adults I prefer spraying the throat to douching as there is less danger of causing an infection of the middle ear. In a few of my cases treated by douching an otitis media set in which may have been due to the douche.

Douching of the nose was not found satisfactory and is not recommended. In six cases symptoms appeared pointing to an infection of the antrum of Highmore, though all these cases cleared up after douching was stopped.

Atomizers/

Atomizers.

Fine sprays of Menthol, Camphor, Thymol, Eucalyptus, &c. were used in a Parke Davis's glaseptic atomizer. They did not appear to have any effect in helping to clear up the condition.

Applications of various solutions on swabs.

This method was found to give very good results in a number of cases, more especially in those cases where infection seemed to be in the tonsil or in the anterior portion of the turbinates. Of all the solutions used silver nitrate 5% to 10% was found the most satisfactory. Swabbing has to be done very carefully so that the antiseptic is applied to all the parts. In cases of tonsils with gaping crypts, if permission cannot be got to remove them, the next best treatment is to pass a fine probe dipped in 5% silver nitrate down each crypt after the cheesy material has been massaged out by the gloved finger.

Some observers claim good results from swabbing with "Argentide" (Silver Iodide 5% watery solution).

Bullman (5) tried the local use of Argentide Colloid 5% applied to the mucous membranes of throat and nose and claims good results. I have used in a number of cases Colloidal Silver put up by Oppenheimer but with no success.

Pyocyanase is of no use in tending to clear away diphtheria bacilli from the throat in late stages.

Thacker (6) claims that he cleared up eight carrier cases in a military hospital at Malta by painting the throats with 50% to 90% silver nitrate after previous cocainizing the parts. The nose he treated by inserting gauze plugs soaked in 1 in 10 ichthyol.

By this treatment he found the throats and noses clear after two applications.

(5) Merck's Annual 1908. page 125.

(6) Thacker, B. M. J. March 11th, 1916.

Administration of Antiseptic Pastilles

This method was given a very extended trial. Wulfing's Formamint and Parke Davis's formalin lozenges were used. One lozenge was given every two hours. In children it was difficult to get them to suck the lozenge, but even with adults when this was properly done the results were altogether disappointing. In no case where diphtheria bacilli were persisting after the seventh week was any positive results got from the use of antiseptic lozenges alone. As well as being non-efficient, lozenges were found to destroy the appetite, and in some cases caused irritation of the stomach. At Knightswood Fever Hospital, Partick, where treatment by pastilles was carried out by Dr. Brown very much the same results were got.

Insufflation of Powders

In a few cases various powders were used in an Insufflator. No success was obtained, however.

Inhalations

Inhalations were not found to be of any benefit.

In the French Army during 1910 carrier cases were treated by inhalations of Iodine, Guiacol and Alcohol. The solution was placed in a dish floated in a basin of boiling water and the patient was set with his head two inches from the dish. Five sittings in the twenty-four hours were given and good results were claimed.

Kuster/

(7) Bischoff. Medical Annual 1915. Dr. Goodall on Diphtheria.

Kuster (8) gives an account of the treatment of Diphtheria and Meningococcus carriers by inhalation in the German Army. The men were treated "en masse" by putting them in an inhalatorium. The disinfectant used contained a hypochloride which gave off chlorine on contact with an acid.

After three visits to the inhalatorium on three successive days the carriers were found to harbour the bacilli no longer.

Although the inhalatorium smelt strongly of chlorine which was present in a free state no ill effects were observed.

(8) Kuster. Deut. Med. Woch. 1915 September 9th.

The second great line of attack was by:-

Surgical Methods

In the majority of cases where the diphtheria bacilli persisted for eight weeks some form of surgical treatment was used if the consent of the patient or the patient's friends was obtained. As in a large number of persistent cases the tonsils were found to be hypertrophied or to be unhealthy, the usual line of treatment was to remove the tonsils and also any adenoids that were present. The operation was usually done under a general anæsthetic. Enlarged tonsils were removed by McKenzie's guillotine or by a Tonsillotome. Flat, unhealthy tonsils were removed by morcellement by Tilley's punch forceps. In my earlier cases one was content to take away just a portion of the tonsil, as it had been suggested that if too much of the tonsil was removed the patient was likely to complain of dryness in the throat afterwards. So far as tending to clear up the persistent diphtheria bacilli in the throat it was found that removing even the smallest portion of the tonsil was often very successful. This was noted also by some of my colleagues at Belvidere, and for some time the view was held there that persistent cases would most likely clear up if a small portion of the tonsil was removed. I still hold this view, though I now think that if the tonsil is removed at all it should be done more radically - in fact the tonsil should be enucleated if possible. For, though the diphtheria bacilli may disappear for a time, a portion of tonsil with gaping unhealthy crypts is often left behind and is an excellent culture ground for other organisms and good lodgment for diphtheria bacilli at a later date. The reasons I give for the disappearance of diphtheria bacilli in those cases where the whole tonsil was not removed are that the diphtheria bacilli were killed off by the inflammation in the tonsil and by overgrowth of other organisms, for/

for example, growth of Staphylococci (See Schiotz's method later on).

Adenoids were removed if present, by a curette and the finger nail.

In nasal cases where the turbinates were found to be enlarged and congested, cauterizing the turbinates was found to be beneficial to the extent that it helped greatly to clear up any persistent nasal discharge. In three cases treated by the cautery and swabbing out with silver nitrate solution 2% the bacilli were found to disappear within two weeks.

Vaccines

Vaccines have been used to a limited extent in an attempt to clear up persistent cases.

At Plaistow Hospital Autogenous Vaccines have been tried in a few cases. The average weekly dose tried there, was 100, 200, 400, 800, 1200, 1600 million. The results have not been completed yet.

Forbes and Newsholm (9) tested Autogenous Vaccines 5/400 millions in Nasal Diphtheria. They found that the rhinitis declined but that the bacilli persisted.

The Russian Gabritschwski (10) has published results in a large number of cases where he injected a vaccine made from a streptococcus derived from the throats of scarlet fever patients and claims that he found diphtheria bacilli in throats clearing away very quickly. He also claims that his treatment was of value as a protective during diphtheria epidemics. He used a concentrated bouillon culture, minimum dose 0·25 c.c. maximum 1 c.c.

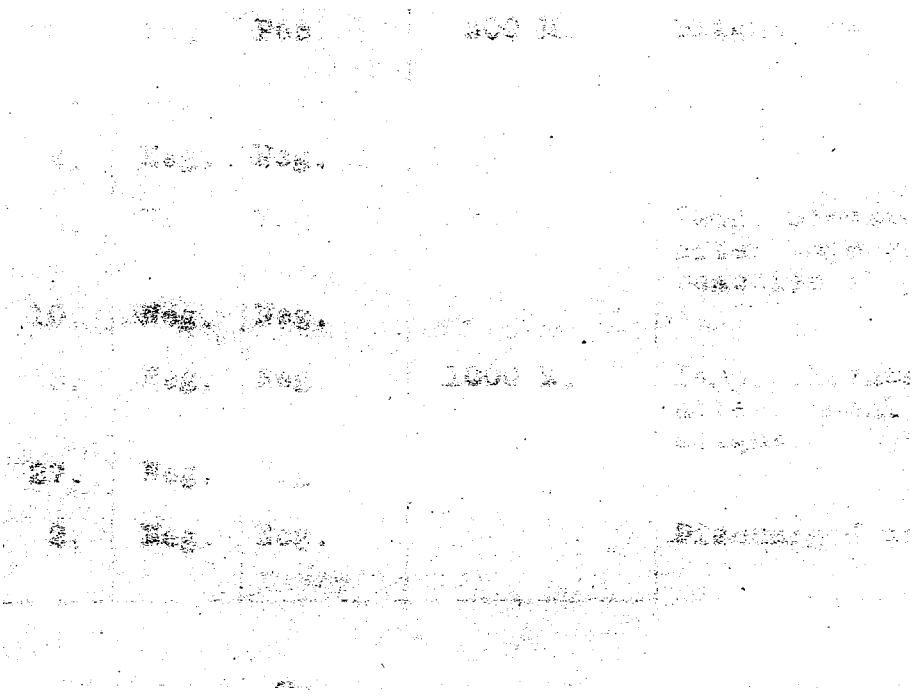
Jockman and Michaelis (11) have tried also the administration of anti-streptococcic vaccine associated with the injections of anti-diphtheric serum going on the supposition that it is the streptococcus which is keeping the tissues in such a state as to harbour the diphtheria bacilli. The results are not conclusive.

(9) Forbes and Newsholm. Lancet Vol. I, 1912. page 294.

(10) Gabritschwski. Brown & Murphy Encyclopædia Med. Treatment. Note on Vaccines.

(11) Jockman and Michaelis. Brown & Murphy. Encyclopædia Med. Treatment. Note on Vaccines.

I now give in detail the treatment of ten cases where I used Autogenous Vaccines. The vaccines were prepared at the Central Laboratory of the Metropolitan Asylums Board under Dr. Cartwright Wood. In each case the patient's own organism was taken and got in pure culture by successive subcultures on blood serum. The pure culture was incubated at 37°C. for forty-eight hours, then emulsified in sterile normal saline. After thorough shaking the emulsion was tested against normal human blood to determine concentration. Counting was difficult. The Thoma Zeiss Pepette and slide is recommended. After the count the emulsion was heated to 60°C. for half an hour and appropriate amounts withdrawn and injected into rubber capped bottles containing 0·5% phenol.



E.M. aged 2½ years, admitted July 30th, Sixth day of disease

Dip. nasal passages. Serum 10,000 A.T.R. 16th day.

Date	Cultures		Vaccine	Notes
1912.	Throat	Nose		
July 30.	Neg.	Pos.		Admitted Profuse Nasal Discharge
Sept. 9.	Neg.	Pos.		
" 21.	Pos.	Pos.		
" 30.	Pos.	Pos.		
Oct. 10.	Neg.	Pos.		
Nov. 13.	Neg.	Pos.		
Dec. 3.	Neg.	Pos.		Profuse Nasal Discharge D.B. virulent.
" 16.	Neg.	Pos.		
" 27.	Neg.	Pos.	100 M.	Slight Local Reaction
Jan. 6.			200 M.	Albumen in Urine on 11th Jan. present 1 day only.
" 15.	Pos.	Pos.		
" 16.			300 M.	Albumen in Urine, Jan. 21st. 1 day only.
" 21.	Neg.	Pos.		
" 25.	Neg.	Few D.B.		
" 26.	Neg.	Pos.	500 M.	Slight Local Reaction
Feb. 1.	Neg.	Neg.		
" 2.	Neg.	Neg.		
" 4.	Neg.	Neg.	700 M.	Temp. elevated 5 hours after injection. Local reaction slight.
" 10.	Neg.	Neg.		
" 15.	Neg.	Neg.	1000 M.	Temp. elevated 32 hours after. Local reaction slight.
" 27.	Neg.	Neg.		
Apr. 2.	Neg.	Neg.		Discharged well.

Summary

Nose cleared up and mucous membrane looked healthy. D.B. remained absent after the fourth injection, but took thirty days to do so.

Dosage 100 to 1000 million.

A.W. aged 3. D.B. found in nose.

Date	Cultures		Vaccine	Notes
1912.	Throat	Nose		
Oct. 24.				Admitted with Measles
Nov. 8.	Neg.	Pos.		Nasal Discharge.
" 29.	Neg.	Neg.		No nasal discharge
Dec. 3.	Pos.	Pos.		
" 8.				Sore on nostril
" 17.	Neg.	Pos.		
" 28.	Pos.	Pos.		Face spotty, slight nasal discharge
Jan. 6.	Neg.	Pos.		
" 11.	Neg.	Pos.		
" 18.	Neg.	Hoffman		
" 19.			50 M.	
" 20.	Neg.	Pos.		
" 24.	Neg.	Pos.		
" 25.	Neg.	Hoffman	100 M.	Slight local redness at injection site. Nasal discharge.
Feb. 1.	Neg.	Neg.		
" 2.	Neg.	Few D.B.	200 M.	
" 3.	Neg.	Pos.		
" 4.	Neg.	Neg.		Nose drier but still moist.
" 12.) " 13.) " 14.)	Neg.	Neg.		
" 17.)				Discharged well

Summary.

Cleared up after three injections taking sixteen days from start of vaccine. Nasal discharge improved but not completely absent on dismissal. Dosage 50 - 200 million.

E.P. aged 6½. Found with virulent D.B. in the nose while in hospital with measles.

Date	Cultures		Vaccine	Notes
1912.	Throat	Nose		
Dec. 10.				Admitted with Measles
Jan. 5.	Neg.	Pos.		Profuse nasal discharge
" 11.	Neg.	Pos.	100 M.	Still nasal discharge and local reaction slight.
" 18.	Neg.	Pos.	200 M.	Ditto.
" 21.	Neg.	Pos.		Nasal discharge less
" 25.	Neg.	Pos.	300 M.	Slight local reaction
Feb. 1.	Neg.	Pos.	500 M.	Temp. elevated two hours after injection
" 8.	Neg.	Pos.	1000 M.	Nasal discharge ceased
" 9.	Neg.	Pos.		
" 10.	Neg.	Pos.		
" 15.	Neg.	Pos.		Vaccines discontinued.

Summary

Remained positive, though nasal discharge entirely disappeared. Dosage 100 to 1000 million.

E.L. aged 5. Dip. throat and nose, fourth day of disease, 12,000 serum. No A.T.R.

Date	Cultures		Vaccine	Notes
1912.	Throat	Nose		
Oct. 2.	Pos.	Pos.		Admitted. Profuse nasal Discharge
" 21.	Neg.	Pos.		Face spotty, sore nose
Nov. 27.	Neg.	Pos.		Condition much the same
Dec. 14.	Neg.	Pos.		ditto.
" 28.	Neg.	Pos.		
Jan. 1.	Neg.	Pos.		D.B. virulent
" 11.	Neg.	Pos.		
" 15.			50 M.	Temp. elevated next day. Slight local reaction
" 25.	Neg.	Pos.	50 M.	Nose moist
Feb. 6.	Neg.	Pos.	100 M.	D.B. virulent
" 13.			200 M.	Nose dry
" 25.	Neg.	Hoffman	300 M.	Local reaction
" 26.	Neg.	Neg.		
" 27.	Neg.	Pos.	500 M.	Slight local reaction
" 28.	Neg.	Pos.		
Mar. 1.	Neg.	Neg.		
" 8.	Neg.	Neg.		Nose dry
" 13.) " 14.) " 25.) " 28.)	Neg.	Neg.		Discharged well.

Summary.

D.B. disappeared after six injections 50 M. to 500 M. Took forty three days, however. Nasal discharge quickly cleared up, after the commencement of vaccines.

D.R. aged 5. Nose virulent. Transfer from Measles Ward.

Date	Cultures		Vaccine	Notes
1913.	Throat	Nose		
Jan. 31.	Neg.	Pos.	50 M. (Stock)	Transfer from Measles Ward. Virulent D.B. in nose. Nasal discharge profuse.
Feb. 10.	Neg.	Pos.	100 M.	General reaction marked. Temp.101 F. Local reaction severe.
" 17.	Neg.	Pos.	100 M.	General reaction marked. Vaccine treatment discontinued.

<u>Summary.</u>

Vaccine discontinued owing to reaction being severe with small doses, ~~being severe~~. Dosage 50 - 100 million.

W.G. aged 1 year 7 months. D.B. of the nose virulent.

Date	Cultures		Vaccine	Notes
1912.	Throat	Nose		
Oct. 24.				Admitted with Measles
Novr. 21.	Neg.	Pos.		Nasal Discharge
" 27.	Neg.	Pos.		
Dec. 21.) " 24.) " 28.) Jan. 5.)	Neg.	Pos.		Nasal Discharge
" 11.) " 12.) " 13.)	Neg.	Neg.		
" 18.	Pos.	Pos.		
" 21.	Pos.	Pos.		D.B. virulent. Report Central Lab.
" 31.	Neg.	Pos.	25 M.	Temp. 99°F. 15 hours later slight local redness and swelling.
Feb. 2.) " 3.) " 4.)	Neg.	Neg.		
" 5.	Neg.	Neg.	50 M.	Slight reaction
" 8.) " 13.) " 15.) " 17.) " 19.) " 21.)	Neg.	Neg.		Discharged well.

Summary.

Negative results after first injection taking three days. Dosage 25 - 50 million.

V.H. aged 3 years and 8 months. Dip. Faucial and Nasal.

Date	Cultures			Vaccine	Notes
1912	Throat	Nose	Ear		
Nov. 25.	Pos.	Pos.			Admitted.
Jan. 8.	Neg.	Pos.	Pos.		Right ear discharging
" 11.	Neg.	Pos.	Pos.		
" 18.	Neg.	Pos.	Pos.		
" 25.	Neg.	Pos.	Neg.		Ear dry
Feb. 1.) " 2.) " 3.)	Neg.	Pos.			D.B. virulent
" 13.	Neg.	Pos.		100 M.	Slight nasal discharge.
" 14.) " 15.) " 17.) " 19.)	Neg.	Neg.			Slight nasal discharge
" 20.	Neg.	Neg.		200 M.	
" 22.					Nose dry
" 25.) " 27.) Mar. 2.)	Neg.	Neg.		300 M.	
" 4.	Neg.	Neg.			Discharged well.

Summary

Cleared up after one dose. Dosage given 100 - 300 million.

W.J. aged 3 years and 6 months. Dip. Faucial and Nasal.

Serum 20,000.

Date	Cultures		Vaccine	Notes
1913.	Throat	Nose		
Jan. 6.	Pos.	Pos.		D.B. virulent
Feb. 14.	Pos.	Pos.		
" 27.	Pos.	Pos.	200 M.	Local redness. No general reaction.
Mar. 1.) " 3.) " 5.) " 7.)	Pos.	Pos.		Slight nasal discharge
" 10.	Neg.	Pos.	400 M.	
" 15.	Neg.	Neg.		Nasal discharge less
" 17.	Neg.	Neg.	600 M.	No nasal discharge
" 19.) " 21.) " 23.) " 25.) " 27.)	Neg.	Neg.		
" 28.				Discharged well.

Summary.

Negative after two injections in 16 days. Nasal discharge disappeared. Dosage 200 - 600 million.

I.W. aged 4½ years. Virulent D.B. found in nose.

Date 1912.	Cultures Throat	Nose	Vaccine	Notes
Nov. 16.				With measles
Dec. 30.				Sore nostrils
Jan. 22.	Neg.	Pos.		
" 27.	Pos.	Pos.		D.B. virulent
Feb. 6.) " 13.) " 17.) " 25.)	Pos.	Pos.		
Mar. 2.	Pos.	Pos.	400 M.	Slight general disturbance with local swelling and thickening.
" 8.	Pos.	Pos.		
" 12.	Neg.	Pos.	600 M.	Local swelling
" 17.	Neg.	Pos.		
" 21.	Neg.	Pos.	800 M.	Some general reaction Local redness nine hours after injection
" 22.	Neg.	Neg.	-	
" 27.) " 29.) Apr. 1.) " 3.) " 5.) " 7.)	Neg.	Neg.		
" 10.	Neg.	Neg.		Discharged well.

Summary.

After starting vaccine treatment D.B. disappeared from the throat within six days and from the nose within twenty days. Three injections in all were given. Dosage 400 - 800 million.

L.T. aged 4 years. Nasal Diphtheria. Serum 10,000.

Date	Cultures		Vaccine	Notes
1912.	Throat	Nose		
Nov. 22.	Neg.	Pos.		D.B. virulent
Dec. 23.	Neg.	Pos.		
Jan. 15.)				
" 31.)				
Feb. 6.)	Neg.	Pos.		
" 11.)				
" 22.)				
Mar. 3.	Neg.	Pos.		D.B. still virulent
" 12.	Pos.	Pos.	150 M.	Slight general reaction. Some tonsilitis.
" 17.)				
" 19.)	Pos.	Neg.		
" 21.)				
" 22.	Pos.	Neg.		Tonsils removed
" 24.)				
" 27.)	Neg.	Neg.		
" 29.)				
Apr. 2.)				
" 10.				Discharged well.

Summary.

Nose negative after one injection but remained in the throat. Tonsils were removed and no positive cultures were got after that.

General Summary of Vaccine Cases.

Vaccines were tried in ten cases; seven girls aged from 1 year 7 months to 6½ years, and three boys aged from 3½ to 5 years.

Seven of the cases had persistent Diphtheria Bacilli in the nose alone.

Three had Diphtheria Bacilli in both throat and nose.

Seven cases cleared up while under treatment. The times taken were 43, 30, 20, 16, 16, 3, 1, days.

In one case treatment was discontinued owing to the vaccine causing a violent reaction.

One case remained positive throughout.

In one case the nose became negative but the throat remained positive until the tonsils were removed.

In all the cases where a nasal discharge was present, the nasal discharge was much improved if not entirely cleared away by treatment.

Treatment of Persistent Cases by Overgrowth of the Diphtheria Germ by other organisms.

The organism which has been most used is the Staphylococcus Pyogenes Aureus.

This method of treatment was introduced by Schiotz of Copenhagen (13) in 1909. He observed that patients with staphylococcal sore throats admitted in error into diphtheria wards did not contract diphtheria, and also that where a convalescent diphtheria patient took a staphylococcal sore throat that the diphtheria bacilli were quickly removed. He then tried spraying the throat and nose in diphtheria cases with a bouillon culture of staphylococcus, and in his first six cases found that the diphtheria bacilli quickly disappeared.

Page of Manilla (14) took up the method and used sprays of twelve hours bouillon cultures every two hours. He found the diphtheria bacilli disappeared in two or three days.

Catlin Day and Scott (15) report eight cases all successful.

Alden (16) used equal portions of three different strains of Staphylococcus Pyogenes Aureus grown on agar, then in broth. He used about 30 c.c. of an eighteen hours' growth. He reports sixteen cases and all but one were negative within a week. The majority only required a few applications.

Rolleston (17) publishes results in ten cases. Six were negative within seven days after starting treatment. Two of the cases were nasal cases and did not give good results.

(13) Schiotz, (A) Cure of Chronic Dip. Carriers in Uskadeliggorelse af. Infectionbaerere ved Diften 1910. (B) Jour. Amer. Med. Assoc. January 29th 1912, page 422 Give summary of (A).

(14) Page, J. Amer. Assoc. 1913, LXI.

(15) Catlin Scott and Day, J. Amer. Assoc. Octr. 28th 1911, page 1452.

(16) Alden, J. Amer. Assoc. 1913, LX. page 1876.

(17) Rolleston, Journal Child. Diseases 1913, X. 298-307.

The rationale of this treatment is not clear. De Witt (18) says there is no antagonism between staphylococci and diphtheria bacilli either in test tube experiments or in experiments on animals.

I give detailed notes on eleven cases treated by this method. The culture of staphylococcus was supplied from the Central Laboratories, MET Asylum Board and was of moderate virulence. Subcultures were made on broth every day. The quantity to be used was measured out into a sterilised atomizer. Parke Davis' glaseptic atomizer was found to be the best for the purpose. The throat and nose were sprayed very liberally. Care was taken not to spray the culture on to the skin of the patient in case one might raise a crop of furuncles.

(18) Lydia De Witt, Journal Infect. Diseases 1912, X. No. I.

L.H. aged 5 years. Dip. Faucial and Nasal, Serum 48,000.

Date	Cultures		Spray	Notes
1912.	Throat	Nose		
Nov. 9.	Pos.	Pos.		Admitted. Profuse nasal discharge.
" 28.				Nasal discharge less
Dec. 31.) Jan. 14.) " 21.) " 28.) Feb. 4.) " 5.)	Pos.	Pos.		
" 25.) " 26.)				Nasal Discharge very much less
Mar. 9.	Pos.	Pos.	30 Min.	Bouillon Culture S.A.P. 25 hours' growth.
" 10.	Pos.	Neg.	30 Min.	Ditto.
" 11.	Pos.	Neg.	50 Min.	Ditto.
" 12.	Pos.	Neg.	50 Min.	Ditto.
" 13.			70 Min.	Ditto.
" 14.	Neg.	Neg.	50 Min.	Ditto.
" 15.) " 16.) " 17.) " 18.) " 19.)	Neg.	Neg.		Throat pale, no nasal discharge. No sores on nose.
" 25.	Neg.	Neg.		Discharged well.

Summary.

The negative result after four sprayings. Duration of treatment ~~four~~ six days.

V.H. aged 5 years 10 months. Diphtheria Faucial. Three weeks before admission.

Date	Cultures		Spray	Notes
1913.	Throat	Nose		
Mar. 3.	Pos.	Pos.		Tonsils enlarged
" 30.	Pos.	Pos.		
Apr. 1.	Pos.	Pos.	60 Min.	48 hours' growth used once a day.
" 2.	Pos.	Pos.	60 Min.	Ditto. used twice a day
" 3.	Neg.	Pos.	60 Min.	Ditto used three times a day.
" 4.	Neg.	Neg.	60 Min.	Ditto.
" 5.	Neg.	Neg.	60 Min.	Slight nasal discharge
" 6.	Neg.	Neg.	60 Min.	Used three times a day
" 7.) " 8.) " 9.) " 10.) " 11.) " 12.) " 13.) " 14.)	Neg.	Neg.		Nose dry
" 17.	Neg.	Neg.		Discharged well.

Summary.

Result after three sprayings was negative, taking three days.

W.M. aged 2 years and 7 months. Dip. Faucial and Laryngeal, 40,000 units Serum.

Date	Cultures		Spray	Notes
1912	Throat	Nose		
Dec. 20.	Pos.	Pos.		Admitted.
" 23.				Throat clean
Jan. 3.				Antitoxin rash
Feb. 8.	Neg.	Pos.		Slight catarrhal tonsilitis
" 21.	Neg.	Pos.		Throat better
" 27.) Mar. 8.) " 15.) " 16.)	Neg.	Pos.		
" 17.	Pos.	Pos.		D.B. virulent
" 28.	Pos.	Pos.		
" 29.	Pos.	Pos.	60 Min.	of 48 hours' growth once a day.
" 30.	Pos.	Pos.		Ditto.
" 31.	Pos.	Pos.	60 Min.	Ditto.
Apr. 1.	Pos.	Pos.	60 Min.	of 48 hours' growth twice a day.
" 2.	Neg.	Hoffman	60 Min.	Ditto.
" 3.	Neg.	Neg.	60 Min.	of 48 hours' growth three times a day.
" 4.	Neg.	Pos.	60 Min.	Ditto.
" 5.) " 6.) " 7.) " 8.) " 9.) " 10.) " 11.)	Neg.	Neg.	60 Min.	Ditto.
" 12.	Neg.	Pos.	60 Min.	Ditto.
" 13.) " 14.) " 15.)	Neg.	Neg.	60 Min.	Ditto.
Apr. 16th to 30th	Neg.	Neg.		Discharged well.

Summary.

Negative result after fifteen days.

W.H. aged 5 years. Dip. Faucial, 24,000 units Serum.

Date	Cultures		Spray	Notes
1913.	Throat	Nose		
Jan. 16.	Pos.	Neg.		Admitted
Feb. 19.				Some nasal discharge
" 25.				Nasal discharge less
Mar. 15.	Pos.	Pos.		Face spotty
" 22.	Neg.	Pos.		
Apr. 5.	Neg.	Pos.		Slight nasal discharge
" 11.	Neg.	Pos.	40 Min. of	48 hours' growth once a day.
" 12.	Neg.	Pos.	40 Min. of	48 hours' growth twice a day.
" 13.	Neg.	Pos.	40 Min. of	48 hours' growth three times a day.
" 14.	Neg.	Pos.	40 Min. of	24 hours' growth once a day (new culture)
" 15.			40 Min. of	24 hours' growth twice a day.
" 16.) " 17.) " 18.)	Neg.	Neg.	40 Min. of	24 hours' growth three times a day.
" 20.) " 21.) " 22.) " 26.)	Neg.	Neg.		Discharged well.

Summary.

Negative result got after six days.

C.K. aged 3 years 4 months. Nasal Diphtheria. Seventh day, 12,000 units.

Date	Cultures		Spray	Notes
/912.	Throat	Nose		
Dec. 7.	Pos.	Pos.		No membrane in throat
" 30.	Neg.	Pos.		Nose dirty
Jan. 15.	Neg.	Pos.		Nose dry
Feb. 3.	Neg.	Pos.		Nose dirty
" 11.) " 18.) " 19.)	Neg.	Pos.		
Mar. 3.	Pos.	Pos.		
" 7.	Pos.	Pos.		Face spotty
" 20.	Pos.	Pos.	30 Min.	22 hours' growth twice a day.
" 21.	Pos.	Pos.	30 Min.	Ditto.
" 22.	Pos.	Pos.	30 Min.	Swabbed on
" 23.) " 24.)	Pos.	Pos.	30 Min.	Ditto. Thick nasal discharge.
" 27.	Neg.	Pos.	30 Min.	48 hours' growth three times a day.
" 28.) " 29.) " 30.) " 31.) Apr. 1.) " 2.) " 3.)	Neg.	Pos.	30 Min.	Ditto.
" 4.) " 5.) " 6.)	Neg.	Neg.	30 Min.	Ditto.
" 7th to 16th	Neg.	Pos.	30 Min.	Ditto. No discharges no sores on nose. Treatment stopped.
" 23.	Neg.	Pos.		

Summary.

Case remained positive.

E.D. aged 2 years. Dip. Faucial and Laryngeal, 16,000 units.

Date	Cultures		Spray	Notes
1913	Throat	Nose		
Jan. 27.	Pos.	Pos.		Admitted.
" 30.	Pos.	Pos.		Fauces clean
Feb. 22.	Neg.	Neg.		Nasal Discharge
Mar. 3.	Neg.	Neg.		Ditto.
" 8.	Neg.	Pos.		
" 9.				Small button removed from nostril.
" 17.) " 18.)	Neg.	Neg.		
" 20.	Neg.	Pos.	20 Min.	20 hours' growth once
" 22.	Neg.	Pos.	20 Min.	Ditto.
" 23.) " 24.)	Neg.	Pos.	30 Min.	20 hours' growth twice. Slight coryza.
" 26.) " 27.) " 28.) " 29.) " 30.) " 31.)	Pos.	Pos.	30 Min.	20 hours' growth three times.
Apr. 1.) to 9.)	Pos.	Pos.	30 Min.	20 hours' growth. Nose bled a little after spraying on three occasions.
" 10.) to 23.)	Neg.	Neg.	30 Min.	No more bleeding. Nose better. No discharges.
Apr. 24.				Discharged.

Summary.

Negative after twenty days.

R.W. aged 4 years. Dip. Faucial, Eighth day, 6,000 units.

Date	Cultures		Spray	Notes
1913.	Throat	Nose		
Jan. 5.) to Mar. 28.)	Pos.	Pos.		
" 30.) " 31.) Apr. 1.)	Pos.	Pos.	30 Min. of	48 hours' growth once a day.
" 2.) " 3.)	Pos.	Pos.	30 Min.	Ditto. twice a day.
" 4.) to 13.)	Pos.	Pos.	30 Min. of	48 hours' growth three times a day. Tonsils slightly enlarged. Some watery nasal discharge.
" 14.) to " 19.)	Neg.	Pos.	30 Min. of	48 hours' growth three times a day, nasal discharge less.
" 23.) to " 25.)	Neg.	Neg.	30 Min. of	48 hours' growth three times a day. No nasal discharge.
" 30.	Neg.	Neg.		Discharged.

Summary.

Negative after twenty one days.

J.R. aged 1 year and 7 months. Measles and Faucial Diphtheria. 12,000 Serum.

Date	Cultures		Spray	Notes
1913.	Throat	Nose		
Jan. 28.	Pos.	Pos.		Admitted.
Feb. 6.) to Mar. 19.)	Pos.	Pos		Sores on nostril.
" 21.) to Apr. 12.)	Neg.	Pos.		
" 15.	Neg.	Pos.	20 Min.	48 hours' growth twice a day.
" 16.) to " 20.)	Neg.	Pos.	20 Min.	48 hours' growth three times a day.
" 21.) to " 24.)	Neg.	Neg.	20 Min.	Ditto.
" 30.				Discharged.

Summary.

Negative after five days.

M.F. aged 2 years. Dip. Faucial and Nasal. Serum 20,000.

Date	Cultures		Spray	Notes
1913.	Throat	Nose		
Feb. 10.	Pos.	Pos.		Admitted. Tonsils enlarged.
Mar. 1.) to Mar. 20.)	Pos.	Pos.		Sores and crusts on both nostrils.
Mar. 21.) " 22.) " 23.)	Pos.	Pos.	60 Min. of	20 hours' growth once a day. Some furuncles about nose.
Mar. 25.) " 26.)	Pos.	Neg.	60 Min. of	48 hours' growth once a day.
Mar. 27.) to Apr. 3.)	Neg.	Neg.	60 Min. of	48 hours' growth three times a day. Some nasal discharge.
Apr. 4.) to " 9.)	Remained Neg.			
" 10.				Discharged.

Summary.

Negative after five applications taking six days.

A.R. aged 4½ years. Dip. Faucial and Laryngeal, 24,000 units.

Date	Cultures		Spray	Notes
1912.	Throat	Nose		
Dec. 9.	Pos.	Pos.		Admitted.
Jan.) to Mar.)	Remained Pos.			Much nasal discharge
Apr. 4.	Pos.	Pos.	40 Min. of	48 hours' growth once a day.
" 5.	Pos.	Pos.	40 Min. of	48 hours' growth twice a day. Slight coryza.
" 6.	Pos.	Neg.	40 Min. of	48 hours' growth three times a day.
Apr. 7.) to " 11.)	Neg.	Neg.	40 Min. of	48 hours' growth three times a day.
Apr. 12.) to " 20.)	Remained Neg.			

<u>Summary.</u>

Negative after three days.

C.B. aged 1 year 6 months. Dip. Faucial and Laryngeal, Fourth day, 60,000 units in three doses.

Date	Cultures		Spray	Notes
1913.	Throat	Nose		
Mar. 10.	Pos.	Neg.		
Apr. 15.	Pos.	Neg.	30 Min.	of 48 hours' growth once a day.
" 16.	Pos.	Neg.	30 Min.	of 48 hours' growth twice a day. Nasal discharge.
" 17.	Pos.	Neg.	30 Min.	of 48 hours' growth three times a day.
" 18.	Pos.	Neg.	30 Min.	Ditto. Ditto.
" 19.) to 24.)	Neg.	Neg.	30 Min.	Ditto. Ditto.
" 30.				Discharged.

Summary.

Negative after five days.

Summary of Staphylococci Cases

Eleven cases of persistent Diphtheria Bacilli in children were treated; five boys aged from 1 year 6 months to 5 years, and six girls aged from 2 years to 6 years.

Seven cases had persistent diphtheria bacilli in both throat and nose.

Three in the nose alone.

One in the throat alone.

Seven of the cases (one pure throat case, two of the nose cases and four of the double infection) cleared up within a week.

Three cleared up entirely within three weeks.

One pure nose case remained positive after a month's treatment.

There were no apparent harmful results. The only complications which arose were mild coryza and mild laryngitis and nasal furuncles.

It is not advisable to use the staphylococcal spray in the early stages of diphtheria before the mucous membrane has completely regenerated, as there would then be a danger of infecting the deeper tissues.

Spraying of Lactic Acid Bacilli.

Wood (19) has used a one or two days' culture on agar washed off by sterile normal salt solution. He sprayed this on to the throat from a sterile atomizer twice a day for a week and reports good results.

Sanford (20) and numerous other American workers have treated the throat with lactic acid bacilli and say that where you get a luxuriant growth of the lactic acid bacilli the diphtheria bacilli are killed off or disappear.

Ten Broeck (21) claims that he has cleared up persistent diphtheria bacilli in throats by infecting the tonsils with the fungus Achlya Muscaris. When the diphtheria bacilli disappear he kills off the fungus by spraying with a weak antiseptic solution.

I have no personal experience of the last two methods but I have noticed that fungi sometimes appear in the throat before the disappearance of diphtheria bacilli. One case I was asked to see in Knightswood Fever Hospital was a nurse who took diphtheria during an outbreak in the Western Infirmary, Glasgow, in 1914. Cultures from her throat had remained positive for over two months, even after the tonsils had been removed. One day a fungus appeared in the growth from her throat and persisted for over a week. After this no more diphtheria bacilli were found in her cultures. I had the opportunity of taking swabs in this case for more than a month after her dismissal from hospital and they all were negative.

(19) Wood, Jour. Amer. Med. Assoc. 1913, LXI, 392.

(20) Sanford, Med. Review of Reviews N.Y. 1913, LXI, P.676.

(21) Broeck, Med. Review of Reviews, N.Y. 1914, LXXXV, P. 49-53

Other methods of treatment which have been suggested lately, but which I have not had the opportunity of trying are as follows:-

Treatment by Diphtheria Endotoxin: Hewlett and Nankiville (22) prepared an endotoxin by growing virulent diphtheria bacilli on serum or blood agar in Roux bottles. The growth was collected, washed two or three times in sterile physiological salt solution by centrifugalizing, so as to remove any adherent toxin. The bacterial mass was then ground in the presence of intense cold by Macfadyen's process, and then the mass was filtered through a Berkfeld filter. The filtrate contained the endotoxin and was standardized by the addition of sterile salt solution to contain from two mgm. to five mgm. per c.c. These observers state that cases of persistent diphtheria bacilli cleared up very quickly under treatment by injection. The bacilli disappeared within a week. As yet this remedy has been very little used as the preparation is not in the market and supplies for the above experiments were prepared privately at the Wellcombe Laboratory, Dartford.

Behring (23) has prepared a new diphtheria antitoxin called M.M.I. This is an emulsion of virulent diphtheria toxin with diphtheria antitoxin in such proportions that the mixture is innocuous to a guinea pig. This is injected into a human carrier case and large quantities of antitoxin appear in the blood after the injection. One case is reported where one-sixteenth of a c.c. of the injection produced 600,000 units of antitoxin where 250 units would have been sufficient to secure immunity.

(22) Hewlett & Nankiville, Lancet. 1912 Vol. I. 143
1912 Vol. I. 292
1913 Vol. I. 1802

(23) Behring Note B.M.J. 1913, May 31st.

Behring recommends inoculation of diphtheria carriers with this new antitoxin to determine the destruction of diphtheria bacilli in the nasopharynx as rapidly as possible. He also states that this antitoxin produces a very much longer immune period than does ordinary antitoxin, and he believes that it may be possible to stamp out diphtheria completely by the prophylactic use of his antitoxin.

Ionic Medication. As it has been claimed that Ionic Medication has been successful in the treatment of meningococcal carriers it might also be tried in diphtheria cases (24).

Hugo (25) recommends an electrode for post nasal ionization.

Radium. The use of radium does not seem to give much hope in the treatment of persistent diphtheria bacilli for according to the work of Chalmers and others (26) even the most powerful radium emanation failed to destroy microbic organisms.

(24) Colebrook & Tanner, R.A.M.C. Journal Jan. 1916. P. 76

(25) Hugo, South African Med. Record, July, 1914.

(26) Chalmers, Arch. Middlesex Hospital, 1912, XXVII.

General Summary and Conclusion.

The conclusion come to is that at present there is no known method by which one can be sure of clearing up persistent diphtheria bacillary cases.

Some authorities still claim that the best treatment of all is by the application of antibacterial solutions and general attention to the patient. Antibacterial agents are certainly the most universally used. They have simplicity and ease of application to recommend them.

Of the various ways of applying antibacterial solutions to the tissues I found that spraying the throat and swabbing the nose were the most successful.

Of the solutions themselves I think silver nitrate solution is the best. Apart from this no one antiseptic seems to be much better than another. Recently I have been using Eusol in the treatment of throat cases but I have not found that it is any better than other solutions.

It is better, however, that some antiseptic treatment should be adopted in treating persistent diphtheria bacilli for the application of an antiseptic probably hinders the growth of bacilli on the mucous surfaces and diminishes their vitality outside the body. So, though we may not be able to kill off the bacteria in the deeper parts, antiseptics are of benefit in limiting the power of infection by their action on the superficial bacilli.

I found that treatment by surgical methods was most satisfactory especially if combined with antiseptics.

Treatment by vaccines does not seem to me to be altogether efficient. In my series of cases I certainly got negative results in the majority of them but the time taken was considerable and it was questionable how much the success was due to the vaccine.

Treatment/

Treatment by overgrowing with other organisms is in my opinion very hopeful. It is worthy of a more extended trial.

The treatment is easy to carry out and if care be taken not to use the spray before the mucous membrane of the throat and nose has regenerated no harmful results are likely to follow.

If it be found that spraying with lactic acid bacilli or by the use of a fungus such as Achlya Muscaris is as satisfactory as spraying with Staphylococcus Pyogenes Aureus then it would be advisable to use the former which are not pathogenic.

Of the other methods of treatment noted (by Diphtheria Endotoxin, Behring's new Diphtheria Antitoxin, Ionic Medication, &c.) it is impossible to give any opinion at present as to their efficiency. A much more extended trial would require to be made.

The problem of the persistent case and the true carrier case is a very real one and is one in which a large amount of work still remains to be done.

The material to work on is to be got in all our large fever hospitals and it would well repay municipal authorities to appoint skilled observers to work on this problem.

REFERENCES.

1. Meikle (XII. 1906) Edin. Med. Jour. XX. P. 510.
2. Nuttall & Smith, Bact. of Diph. 1908. P. 420.
3. Sims Woodhead, Met. Asylum Report 1901. P. 271.
4. Beyer, Munch. Med. Wochenschr, 1913, LX. No. 5.
5. Merck's Annual, 1908. P. 125.
6. Shacker, B.M.J. March 11th, 1916.
7. Bischoff: Goodall's review Diph. Medical Annual 1915.
8. Kuster, Deut. Med. Woch. 1915, September 9th.
9. Forbes & Newsholm, Lancet, Vol.I, 1912 P. 294.
10. Gabritschwski, Brown & Murphy Encyclo. of Med. Treatment Note on Vaccines, 1915.
11. Jockman & Michaelis " " "
13. Schiotz, (A) Cure of Chronic Dip. Carriers in Uskadeliggorelse af. Infectionsbaerere ved Diften 1910. (B) Jour. Amer. Med. Assoc. Jan. 29th 1912 P. 422 gives summary of A.
14. Page, J. Amer. Med. Assoc. 1913, LXI.
15. Catlin Scott & Day, J. Amer. Med. Assoc. Oct. 28th 1911 P. 1452.
16. Alden, J. Amer. Med. Assoc. 1913, LX. P. 1876.
17. Rolleston, Jour. Children's Diseases 1913, X. 298-307.
18. Lydia De Witt, Jour. Infect. Diseases, 1912, X. No. I.
19. Wood, Journ. Amer. Med. Assoc. 1913, LXI, 392.
20. Sanford, Med. R. of Reviews, New York, 1913, LXI, 676.
21. Broeck, Med. R. of Reviews, New York, 1914, LXXXV. 49.
22. Hewlett & Nankiville Lancet, 1912, Vol. I, 143.
" 1912, Vol. I, 292.
" 1913, Vol. I, 1802.
23. Behring, Note B.M.J. 1913, May 31st.
24. Colebrook & Tanner, R.A.M.C. Journal, Jan. 1916. P. 76.
25. Hugo, South African Med. Record, July 1914.
26. Chalmers, Arch. Middlesex Hosp. 1912, XXVII.

I certify that the books or papers quoted were all personally consulted by me, with the exception of 4 + 8.

A. Stevenson.