OBSERVATIONS ON THE PROBLEMOF THE DIPHTHERIA "CARRIER":-

A Clinical Study of Fifty Consecutive Vaccine Treated Cases.

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A short account of the circumstances which prompted the undertaking of some investigations into a difficult problem may be of interest and will serve to introduce the subject-matter formingthis thesis.

An adult male patient was admitted to one of the wards certified as suffering from diphtheria.

The following history was given:-

A child of this man had sickened of throat trouble. A physician was called in who recognised the condition to be one of typical faucial diphtheria.

On notification of the case to the Sanitary Authorities, the child was promptly removed to the Isolation Hospital.

As a result of the routine examination of throat swabs from the "contacts" namely, the mother and remaining children, it was discovered that two other members of the family were harbouring the B. diphtheriae.

They likewise were sent to Hospital.

When/

When the above throat swabs were taken, the father was "out at work". A culture from his throat was consequently not obtained.

On the evening of the day on which the results were made known, he "took it into his head" to pay his physician a visit to"have his throat tested".

This action, it must be noted, was taken simply and solely to satisfy personal curiosity.

Subjective and objective phenomena were entirely absent. He complained of nothing and "was in better health than he had ever been in his life".

None the less, the culture from his throat yielded practically a pure growth of typical diphtheria bacilli.

As a result of this finding, he, in turn, was reluctantly compelled to follow the others to Hospital and/

and on arrival was in a most unhappy and unpleasant frame of mind. He manifested his chagrin by taking exception to everything and everybody with whom he came into contact.

It was with difficulty and only after the medical and nursing staffs had been subjected to his abusive attacks that he permitted a small dose of antidiphtheritic serum to be given subcutaneously.

It was thus realised that there had been admitted a really "troublesome" patient.

Thereafter, the daily ward-visits were made unpleasant by the tireless reiteration of his woeful plaint and only after much coaxing was he prevailed upon to remain in bed for twelve days - the irreducible minimum in respect of safety from serum complications.

A hope was entertained that when the patient was allowed up, the greater freedom of action secured would act/

act as balm to his wounded feelings.

There was no such happy result.

He remained a malcontent.

Naturally, by this time, the character of the bacteria inhabiting his tonsils was of more than ordinary interest. Therefore, unusually early in his residence, throat swabs were taken with a view to procuring the regulation "two negatives".

Once again, fate was against him, as he persistently cultured "positive" for weeks on end.

Now the patient was desperate, and, as his wife had taken ill, there were the usual accompanying monetary embarrassments.

He pled that he was the wage-earner, that he was being compulsorily detained "for no earthly reason" and that not that way lay economic soundness.

It is uncommonly difficult to impress a labouring lay-

man/

layman with arguments about preventive medicine altogether based on bacteriological niceties.

Practically all the medicaments that are or ever were credited with usefulness in this connection were tried, but only after he had burdened the ward with his sullen presence for ten weeks, were the requisite "negatives" obtained to warrant his dismissal. His parting taunt when leaving was, "if that's a' medicine can dae for a man efter a' thae years, then ye should be ashamed o' yersel ".

On reflection, the truthfulness of his implication was conceded. Careful consideration of his point of view forced one to the conclusion that the absence of an infallible cure for a man in his condition was a sad commentary on the physician's helplessness. His sweeping condemnation of the profession seemed a challenge well worthy of acceptance, especially as it crystallised the views of many other patients who, in a previous experience, had been equally unwilling victims but had not given such/

such free expression to their sense of injustice.

The state of affairs obtainingin this case was that an able-bodied healthy man was condemned by law to indefinite detention, because of the presence in his throat of organisms of microscopical dimensions. These were not producing any self-evident local or general manifestations, and the "carrier state", as a force to be reckoned with, was beyond his comprehension. Coupled with this was a very natural soreness on realising that he had quite unnecessarily submitted himself to examination and thereby needlessly made himself liable to all the distasteful consequences of a "positive" finding. His wrath was not allayed by the knowledge that many others, although similarly affected, were "walking about" without interference.

At the risk of being charged with irrelevancy, an attempt has purposely and at length been made to convey some idea of the attitude of the layman towards this problem.

An appreciation of/

of it is helpful towards granting the necessity and justification for the employment of every means which can be proved to afford success in the treatment of the condition.

If it is granted that this irksome and apparently unnecessary and purposeless detention is a very potent factor in causing unrest amongst hospital patients of the adult type above described, there will have been created, in some measure, the mental atmosphere most favourable for vigorous pursuit of a trustworthy remedy.

It will be well to survey broadly the field of past experience bearing on the subject, that by a study and review of the origin and lines of progress so far recorded, it may be ascertained what progress has been made, what is sure ground, and what is quagmire and therefore to be avoided. Such a retrospect will entail bacteriological, therapeutic, and economic considerations and procedures, and, although the bibliography of diphtheria is ponderous and much of it not apposite to the

purpose/

purpose in view, a knowledge of what has already been done with respect to the treatment of "positive throats" is an essential preliminary to outlining any further mode of attack.

The discovery of the bacillus first described by Klebs in I883, and further investigated by Löffler in I884 was epoch-making and of inestimable value to mankind. Whereas, previously, all treatment was necessarily empirical, thereafter, interference was perfectly definitive, scientifically accurate, and specifically directed.

None the less, the consequences of this new-found knowledge, although not in any measure discounting the undoubted advantages which accrued, were unforeseen and, in one respect, unfortunate for the patient. So long as the causal agent was unrecognised, the problems of the "carrier" and the "positive throat" were non-existent. Such victims as previously survived the initial attack and subsequent paralytic period had, at any rate, the satisfaction of being pronounced free from danger to themselves and/

and others after a reasonable period of convalescence.

Nowadays, thanks to the universal and earlier recognition of the local lesion and the more or less prompt exhibition of antidiphtheritic serum, the initial periods of the disease have mercifully been shorn of many of their horrors. It is an odd reflection, however, that, "pari passu" with the benefits accruing from the recognition of the cause, untoward late effects may obtrude themselves. Just as there now exists the certainty of early and comparatively faithful recognition of a particular bacillary presence, so equally, but with less satisfaction, late and unwelcome persistence of the undesirable alien may be demonstrated.

It will be conceded that the relevant literature, subscribed by the recognised authorities, reveals a remarkably chaotic and unsatisfactory state of affairs. Quotations of their views, opinions, practices, and experiences will repay perusal/

perusal as, thereby, a very complete understanding of the position in relation to the prevention of this infectious disease, will be arrived at.

I. No less an authority than Ker has it that:-

> "The isolation"of patients suffering from Diphtheria" should be maintained until at least two consecutive negative cultures have been obtained from the throat. A long time is often required before this is attained. Should the bacilli persist for many months, perhaps the best plan is to test their virulence on small animals, and if they are non-virulent, to dispense with further isolation, but to make cultures at intervals and direct the patient to continue local antiseptic treatment as long as the positive results are obtained. Persistence of the bacilli is most likely to be met with when the tonsils are large and ragged. Meikle, investigating the condition of the throat in patients discharged from the Edinburgh City Hospital found that in about 80% of the cases in which bacilli were present at the date of discharge the tonsils were considerably enlarged. No one antiseptic was found to be more efficacious than another for throat treatment, but an attempt should always be made to get rid of the organisms by local applications, unsatisfactory as these too often are. The rarity of return cases/

cases of diphtheria in Edinburgh (no case has ever resulted from a patient known to have bacilli in his throat on the day of discharge) led Meikle to conclude that in the vast majority of cases the germs are probably not virulent. In those cases in which the virulence was tested on animals his results were negative.

It may be added that the presence of Hofmann's bacillus in the throat of a contact is regarded by some authorities as suggestive. The isolation then, of the carriers of this bacillus is probably advisable in a school or ward epidemic."

With reference to the foregoing, it is to be remarked that, although the uselessness of local antiseptic applications is frankly admitted, in the regrettable absence of anything more effective, their vigorous routine employment is nevertheless advocated.

The very multiplicity of so called "cures" is an admission of their comparative worthlessness.

At various times, the following amongst many others have been pressed into service as curative agents:- carbolised glycerine of varying concentrations, formaldehyde, chloramine T/

chloramine T, flavine, urea, papayotin. None of them appears to do much more than inhibit the growth of those organisms with which it may come more immediately into contact.

The writer, after extended trial, concludes that formaldehyde is most reliable as, with care and thoroughness, 25 per cent of cases so treated become "negative" after longer or shorter periods.

The method employed was to make up solutions containing 0.25 per cent, 0.5 per cent, 0.75 per cent, and I per cent, and to apply these on swabs to the fauces thrice daily. Commencing with the weakest concentration, the next highest was employed each succeeding day, the I per cent solution being repeated on the fifth day. On the sixth day the throat was untreated, and a culture was taken on the seventh. Frequently this proved negative, but seldom indeed was it possible to obtain a second, much less a third "negative". Failure in the first instance merely indicated a repetition of the/

the course of treatment.

These procedures were tedious, indeterminate, and irritating to the patient who could not be expected to appreciate the wisdom of persisting with a disagreeable and oft-repeated interference which was only productive of further "positive" results.

The treatment of "carriers" and "positive throats" as out-patients, referred to by Ker, must necessarily be cumbersome and unsatisfactory. Few people would not tire of daily gargles and weekly visits to a bacteriologist especially when indefinitely continued.

The conclusion that the vast majority of these cases harbour avirulent organisms is merely an expression of opinion but no statement of fact.

It has been a common experience in the Glasgow Fever Hospitals to have "positive" patients whose cultures proved persistently virulent to the guinea-pig. This test was naturally/

naturally much in demand as, on its "avirulent" finding lay the hope of so many. Unfortunately, the experiment necessitates obtaining in pure culture the organism to be tested. When it is realised that the very microscopical "fields" creating doubt are those in which the bacilli are few and far between, it will be conceded that the bacteriologist's task is not a simple one. He may sub-culture unsuccessfully for days, ultimately to find overgrowth of more vigorous cocci. In these circumstances a further specimen must be obtained and another week is therefore lost before a finding is arrived at. If a report be made ten or fourteen days after submission of the specimen, the clinician will have little cause for complaint.

To most patients, three weeks in late convalescence are peculiarly "long" weeks but, if Meikle's conclusion were infallible, namely, that "the germs are probably not virulent", they might be tolerated. Unfortunately, no promise of

certain/

certain liberation need be made as, in the vast majority of cases, disappointment must result.

Finally, if the presence of Hofmann's bacillus is to be "regarded as suggestive", there is presented a situation which is singularly hopeless.

This matter will be referred to later.

Meanwhile, in pursuit of the study of the literature, Osler may be cited, who says:-

> "Following an attack of diphtheria the bacilli may persist in the throat or nose after all the membrane has disappeared for weeks or months - even fifteen months. In explanation of this persistence Councilman has called attention to the frequency with which the antrum is affected. It has been shown by numerous observations that, after all the membrane has cleared away, virulent bacilli may persist in the throat from periods ranging from six weeks to six months or even longer. There is evidence to show that the disease may be communicated by such patients, so that isolation should be continued in any given case, until the bacteriological examination shows that the throat is free. Careful attention should be/

be given to the throats and mouths of children particularly to the teeth and tonsils, as Caillé has urged. Swollen and enlarged tonsils should be removed."

Osler notes and admits the unsatisfactory state of our knowledge in this particular. He seeks, however, to indicate the possibility of successful management by general attention to mouth hygiene. In this connection, a somewhat motable case in the writer's experience comes to mind:-

It was of a child, an inmate of a Poor Law Institution, who was admitted to hospital suffering from faucial diphtheria. This patient remained in hospital for twelve months and was "positive" at the end of that time. Her mouth was given every attention. To this end, such preparations as boroglyceride and glycerine, listerine, chlorine water, hydrogen peroxide, corrosive sublimate, were used. As a last resort, tonsillectomy was performed. Her"swabs" remained as "positive" as formerly.

It would appear from above case and from many others which might be quoted, that care of mouth, teeth, throat and tonsils/

tonsils, "per se", is insufficient to ensure success.

For a possible explanation of the persistence of the bacilli, in the face of antiseptics and in spite of tonsillectomy, vide p. 90.

3. The next reference is to M'Vail who states that:-

"The vitality of the organism in the human throat is very great. Sometimes it is found three months or later after the throat looks clean, though customarily it disappears in a week or two. Though its life is not very active, its infective power often persists. A discharge from the nostrils containing infective bacilli may continue for months. Of still more importance is the presence of the microbe in the throats of "contacts" who have not themselves any clinical symptoms of the disease. Massachusetts Association of Boards of Health have concluded that at least I% or 2% of sound persons in the general public in towns and 8% to 50% of exposed persons have the Klebs-Löffler bacillus in their throats. Probably the bacillus is virulent is less than a fifth of such cases (Welsh and Schamberg) On the other hand, there is a quite appreciable number of cases in which the disease is actually present without the appearance of any membrane on the throat, the toxic phenomena being/

being due to B. diphtheriae in the lung, spleen and elsewhere. Dr. Davies of Bristol has recorded his experience that at one time in the same town the type of B. diphtheriae may be distinctly different from that found at another time and that these differences of type are accompanied by a different habit of the disease, both as to fatality and infectivity. One type is short, thin, usually pointed at one end and staining either solid or in granules. The fatality of disease caused thereby is singularly and consistently low. The other type is long, round-ended, beaded or granular. This causes a virulent variety of the disease. There are American records of differences of bacillary type in different towns at the same time. The essential bearing of such facts on the spread of diphtheria is manifest".

M'Vail is cited to lend confirmation to the before mentioned contentions.

All indirect methods of infection presume the presence of a direct mediary so that, whatever percentage of the whole may be deemed to be virulent, virulence must exist. Otherwise, it would be impossible to account wholly for the spread and propagation of the disease.

It may be noted that M'Vail, unlike Ker and Meikle, attaches

importance/

importance to the presence of the bacillus in nasal discharges but, more so, to its persistence in the throats of those "who have not themselves any clinical symptoms of the disease". He recognises such individuals to be very potent factors in the etiology of clinical diphtheria.

Thus early appears evidence of that difference of opinion amongst authorities, the existence of which presented a considerable hindrance to the successful prosecution of the present investigations.

The observation of Davies of Bristol, regarding variations in type, accords with the writer's experience and is of interest epidemiologically.

The attempt will be made to demonstrate that the organisms of lesser virulence are attenuated forms of their more elongated brethren and that such influences as habitat, nourishment, temperature, and moisture determine malignancy. Many of the films prepared after vaccination show well defined degenerate forms/

forms corresponding with those recoverable during benign epidemics.

Considerations of the disease-spreading propensity of "carriers", of the morphological peculiarities of the B. diphtheriae, and of their associated malignancies, will be dealt with in their proper context.

4. Further, Osler and M'Crae in their volume declare that:-

> "no satisfactory means have been found of ridding carriers of bacilli. Tonsillectomy, adenectomy and removal of foreign bodies and carious bone have been followed by rapid cure. Local applications designed to benefit the underlying disease of the mucous membrane are of more value than antiseptics directed against the bacilli. Although chronic, nasal diphtheria will often clear bacteriologically as soon as the slight toxin irritation is eliminated. Schiotz reported a cure from spraying the throat with pure cultures of staphylococcus aureus and several have confirmed his results. De Witt could find no bactericidal action from the staphylococcus or its products and its action is supposed to be by displacement or overriding. No results have followed its use in twelve virulent and avirulent "carriers" in our wards. Hewlett and Nankwell have reported/

reported cures in from four to thirty-three days in twelve out of eighteen "carriers", mostly complicating scarlet fever They used a solution of bacterial substance prepared by grinding the bacilli in intense cold and filtering. Of twelve "carriers" in our wards, four became negative in two weeks by the use of diphtheria vaccine, in doses of I-IO millions every 4-6 days. Petruschky reported the treatment of six cases with injections of diphtheria bacilli killed by chloroform gas. Four of the cases were treated during early convalescence, and became negative in five to twenty-nine days, one of the other (bacteriological) cases became negative only after over a year of intermittent treatment".

It had long been a matter of vital interest to discover if there might not be some constant bacterial association in the throats of "carriers".

Problems of symbiosis and saprophytism had been fascinating studies, and it appeared reasonable to assume that investigation along such lines might lead to definite findings.

In fact, the diphtheria-vaccine treatment of "positives" applied in the series of cases about to be reviewed, was the direct outcome of failure to recognise any such constant association/

association. Had the hope materialised, the intention was to employ either a specifically made vaccine or one of the marketed antistaphylococcal or antistreptococcal vaccines against the supposed abetting organism. By the removal of thislatter, it was confidently anticipated that the persistent B. diphtheriae would simultaneously disappear.

The premise, that a pyogenic organism would be inculpated, appeared justifiable from the clinical observation that those cases are invariably most toxic whose local membranous lesion has marked and demonstrable pyogenic associates.

In this respect also, it may be stated that diphtheria, complicating any of the following:- scarlet fever, measles, whooping-cough, catarrh of the respiratory tract or lungs themselves (from whatever bacillary cause arising), is not only a common association but, in the vast majority of cases, predicates a more than usually severe invasion.

It may be worthy of remark that the diseases enumerated are/

are, "par excellence", notorious for their association with all manner of pyogenic and other organisms.

Realising the apparent impossibility of success in the "associate" quest, the idea of using a vaccine of the offending organism itself appealed to the writer, and was forthwith put in practice, quite independently of the knowledge of its previous tentative employment. Forty-three consecutive cases had been successfully treated when interest was sufficiently aroused in the matter to consult the literature on the subject. The figures and facts to be stated later will prove the superiority of the results over those given above, namely:- "four out of twelve carriers".

It may be noted in passing that there is no explanation given as to how the vaccine was prepared nor information whether the same one was used in all. It is equally indefinite as to whether the twelve received vaccine and four only responded. In any case, probably on account of the manifest poorness of the results/

results, the practice does not appear to have been continued.

The following quotation is somewhat lengthy, but as the work from which it is taken is thoroughly up to date and notes clearly and impartially mostly every modern expedient used or suggested for use in the particular condition under review, one may take the liberty of quoting in full.

5. "Antibacterial Serum:

"Antitoxic serum does not tend to kill the bacilli which cause diphtheria. They will grow readily in the fluid itself, and continue to exist in a virulent form in the throats of persons who have been injected with antitoxin.

6. Wassermann claims to have succeeded in the production of a serum which is bactericidal. He prepares a fluid somewhat analogous to Koch's "new tuberculin", by pounding up the bacilli and extracting them with ethylene-diamine, 20c.cs. of this solvent being added to I grm. of pulverised bacilli. The mixture is well shaken in a special apparatus. and is then submitted to the centrifuge. The supernatant fluid is of a yellow colour, and contains the intracellular toxins of the bacilli. It is capable of killing rabbits when injected into them. If, however, the toxin is mixed with a proportion of antitoxin and repeatedly injected into these animals, the serum obtained from them is strongly agglutinative/

agglutinative of diphtheria bacilli. Wassermann thinks that this serum will afford a means of distinguishing B. diphtheriae from pseudo-diphtheria bacilli, and that it
7. may possibly have curative properties. Concetti writes in favour of the use of anti-bacterial serum as an adjunct to antitoxin, and as a local application to the throat in the form of lozenges. A"bi-valent"(antitoxic and antibacterial) serum may also be used prophylactically, as well as for irrigation of the nostrils to avoid spread of infection to the nose; for local application to the trachea after tracheotomy (2.5 c.cs. every three hours)
8. and in conjunctival diphtheria (Bandi).9. Dopter advises the local use of antitoxic serum in the form of lozenges; but the serum is theoretically inferior to the bi-valent serum. He also uses insufflations of powdered dry serum for nasal diphtheria, and finds this procedure of some value, but less so than in faucial cases.

Vaccine Treatment:- Possessing, as we do, in antitoxic serum a remedy at once so potent and so reliable, and, one, moreover, which has the overwhelming advantage of being available at a moment's notice, it is not surprising to find that diphtheria vaccine has not been employed to any large extent. At the same time, vaccine treatment is of distinct value in those infections which become chronic, and in which the/

the responsible organism remains domiciled in the throat or nose for prolonged periods after the acute clinical symptoms have been entirely removed by the employment of antitoxin ("carriers"). In such cases a vaccine should be prepared from that strain of B. diphtheriae actually infecting the patient, the bodies of the bacilli carefully washed free from toxin, the vaccine then standardised, and administered in doses of five to ten millions at intervals of three to five or seven days. In our experience one to two injections are usually sufficient to ensure the disappearance of thebacilli from the local site of infection.

10. Hewlett uses for the same purpose endotoxin, obtained from the diphtheria bacillus by grinding at the temperature of liquid air, in doses of 0.5 mg."

Than the foregoing, it must be conceded that it would be difficult to furnish a better example of scientific ingenuity.

It is noteworthythat substances have been produced partaking of the nature of lozenges, insufflations of powdered serum, media containing bacilli, killed in one case by exposure to chloroform gas, in another, pulverised at the temperature of liquid air, and, in a third, extracted by ethylene-diamine and submitted to further tedious processes. The claims made

by/

by the several investigators are seldom extravagant and usually consist of the expression of opinion that their employment "may possibly have curative properties".

Vaccine treatment, mentionedrather as a postscript, is not unduly obtruded and, the recommendation that it should be "autogenous and washed free from toxin",- that it should contain living organisms,- makes its application unattractive and its general availment extremely problematical.

Diphtheria, like tetanus, is a disease where characteristically the causative bacilli reside locally. The effects of their presence, as manifested by the patient, are esentially produced by the toxin-absorption therefrom. Except in the rare caseswhere the disease is of the haemorrhagic malignant type there is no bacillaemia. Put briefly, if there were no toxaemia, there would be no such thing as clinical diphtheria. The injection then of a substance containing living B. diphtheriae, so as to make their access to the blood stream possible, appears to court the production of just such a bacillaemia as is recognised to be of the gravest significance.

Again, in the main, vaccine therapy has found its most useful application in such local conditions as acne, boils, gonococcal joint infections, and others. Its use in more general infections, such as the septicaemias and enteric fever, has usually been less favourable.

Now, patients with "positive" throats for the B. diphtheriae, being sufferers from an admittedly local infection, it appeared reasonable to treat them along lines which had been proved useful in comparable conditions.

The justification for the injection of dead cultures of an organism is based on the view taken by Wright that, while the local capacities for resistance may have been lowered, resistance mechanisms in other parts of the body have not been brought into play. The vaccine is considered to stimulate these so that the region, in which bacillary growth and multiplication occurs, is flooded with antibacterial bodies.

The vaccine used in the present experiments was prepared differently/

differently from that indicated above. The necessity for autogenous vaccination was proved not to exist, hence the production of a large amount of stock vaccine obviated the necessity for laborious laboratory work and made its use immeasurably more practicable.

After all, the necessary facilities for the elaboration of complex media are not given to everyone who has to work with such cases, nor can the requisite technical skill on the part of the administrator often be presumed. On the other hand, the material used in the following cases might quite readily be produced centrally and distributed much in the same way as is practised with antidiphtheritic serum itself.

Unquestionably, availability, coupled with ready and easy administration are the criteria by which any therapeutic measure must be judged. Only in so far as these are present will general favour be bestowed on it.

It is scarcely necessary to suggest that, if antidiphtheritic serum/

serum required to be autogenous (as obtains in scarlet fever) and, if every physician, who to-day considers its administration as a simple routine practice were called upon to take in hand its manufacture, diphtheria would not claim for itself the finest results in the whole field of serum therapy.

Antidiphtheritic serum or diphtheria antitoxin is, as its name implies, antitoxic. There is no antibacterial element in it - hence lethal influence upon the bacilli is not afforded nor can it be expected. The present treatment consists merely in providing the victim with artificial antibody in the shape of antitoxin and, having thus established a barrier against the devastating blood-borne toxin, to rest content. Manifestly, inasmuch as only the effects have been treated, only part of the problem has been solved. The cause, namely the organism, is unaffected. Therefore, it would appear logical to supplement antitoxin administration by the subsequent addition of artificial antibacterial substance. It is pled, that there is a necessity for supplying just such antibacterial substances as/

as will complement antitoxin, thereby completing the defences of the human economy against this particular bacillary invasion.

II. Lastly, from the "1917 Medical Annual" there is transcribed the following:-

> "W.H.Park and A.Zingher report on the results of immunisation with a toxin-antitoxin mixture. These researches have led them to the following conclusion. For the general prophylaxis of diphtheria in schools and communities, excluding immediate contacts, a mixture of toxin-antitoxin alone, or toxin-antitoxin plus vaccine of killed diphtheria bacilli is recommended. The dose is I c.c. of toxin-antitoxin and I,000 million bacteria injected subcutaneously and repeated three times at intervals of six orseven days. Sufficient time has not as yet elapsed to judge the value of adding the injections of the bacilli to the toxin-antitoxin".

Again, no mention is made as to whether or not the vaccine recommended was autogenous. If it were autogenous, it can only be repeated that the means advocated would represent an overwhelming proposition in practice.

Also/

Also, the dosage appears enormous, especially for prophylactic administration and, sofar as the writer's experience has gone, apparently immoderate. To make vaccinesof concentrations per c.c., as above indicated, would entail such an expenditure of labour, time and money, as very effectually to put their general employment far outwith the province of routine practice and practicable therapeutics. With the knowledge that passive immunity, although variable in its duration, is, at the best, comparatively short, (probably not more than one to five weeks) and, that even active immunity, conferred in the manner stated, is of longer duration, the pronouncement that "sufficient time has not as yet elapsed to judge the value" etc. is unconvincing.

Further, it has been conclusively proved experimentally that repeated injections of antitoxin have no cumulative effect as regards immunisation. In any case, Park and Zingher admit that the number of cases observed - (which number/

number is not stated)- was too small to allow of a decided statement.

Although the writer's opinion of the microscopical appearances was based on a previous experience of over five thousand examinations of similar films, the very nature of the investigations suggested the advisability of seeking confirmation of the results. Throat swabs from the treated patients and occasionally from the untreated were therefore submitted for the opinion of a recognised bacteriological authority. Although, in the majority of instances, complete agreement was reached,in a minority, differencewas recorded. On every occasion, the discrepancy arose from the respective interpretations put upon atypical bacilli. These latter, from their morphological appearances, staining reactions,and distribution, the writer characterised as B.Hofmann, in contradistinction to the secondary opinion which/

which placed them "positive" for the B. diphtheriae.

This lack of unanimity produced more or less delay with some of the earlier cases for, deference to accredited opinion counselled dismissal unwise until agreement was reached. Such early experiences, however, were not repeated, for, submission of the disputed organism to an early physiological test definitely revealed its nature. It is satisfactory to record that the bacilli, although originally characterised as "positive", in no case proved lethal to the guinea-pig.

Ready confirmation of the nature of the microscopical appearances was forthcoming in the very application of the vaccine itself. This latter was specific in character. It contained only B. diphtheriae and, in no instance, was it contaminated with B. Hofmann. It was purposely monovalent, not divalent nor polyvalent, so that it was concluded that an organism whichremained unaffected for even a short space of time/

time was unlikely to be B. diphtheriae. That such a process of reasoning by exclusion was logical and warranted, the animal test has not so far disproved.

It is a platitude to point out the difficulty in general of judging the value of a particular method of treatment, increased in the case of vaccines by the fact that treatment has been allowed to remain largely in the hands of the men without clinical experience. Moreover, for vaccine treatment to be effective, accurate bacteriological diagnosis is a preliminary requisite. It is just precisely in this one particular that vaccination in diphtheria presents unusual and unique difficulties.

This feature will be further alluded to but, in passing, it will be wise to take note of the following considerations for, it behoves an intruder towalk warily in a domain where there is diversity of opinion amongst bacteriologists themselves, coupled with disagreement as to the interpretation to be put upon/

upon well recognised variations in morphological appearances of such a well established organism as the B. diphtheriae.

Whereas, the pneumococcus is the pneumococcus the wide world over, the B. diphtheriæ is less universally accredited. The practical outcome of this indefiniteness is that the consultative bacteriologist, he who is the approved authority to the Sanitary organisations of our counties and larger towns, is more and more compelled to adjudicate for safety. Given a collection of throat swabs of unknown origin, it is not unnatural that he should view with grave suspicion any and every bacillary form that may present on cultivation. He is very conscious of the fact that the physician who submitted the swab for his examination was prompted to do so by reason of the presence of more or less suggestive clinical signs and symptoms of diphtheria inthe subject's throat. There is also, in the very nature of things, the impelling necessity for immediate judgment. It cannot be wondered at then if, to guard against/

against the calamity of one "missed positive", several "doubtfuls" are included amongst those who eventually reach hospital notified as diphtheria. Both must be given serum and that immediately. Thereafter, the wrong done cannot readily nor conveniently be undone.

Administrative considerations are opposed to admittingthe wisdom of different departments of the same service being at variance.

In like manner, dependence upon a third party for authority to dismiss convalescents, is apt to prove disheartening.

Here again, the necessity of the situation prompts the latter to "positive" pronouncements when, were the origin of the "swab"known, interpretation of appearances in the resulting film would lead to a modified if not a different opinion.

The truth of this contention has been proved more than once for, it was no new experience to have a culture, personally reckoned "negative", reported "positive" and also, days afterwards, pronounced/

pronounced avirulent on animal inoculation.

Such contradictory reports, of course, could never be made if discrimination were exercised in judging as to the real significance to be attached to the various bacillary forms infesting the fauces.

Sweeping condemnation of everything which has the misfortune to be rod-shaped is not only unscientific but unjust. At the same time, it must be admitted that, in the present uncertain state of our knowledge, the application of corroborative tests to "cultures", submitted in the first instance, is impracticable. The B. diphtheriae brooks no delay and will certainly not cease its malign activity whilst investigators laboriously pursue the study of its microscopical and cultural characters, its sugar reactions and, if need be, its degree of virulence to the guinea-pig. All of these procedures involve the loss of that valuable time which, if not effectively employed, spells disaster to the host.

This/

This same disability applied to the reports upon the "swabs" of convalescents and, though only less compromising, was none the less irksome and merely confirmed the necessity for the employment of some method which would afford a reasonably assured means of "negativing" swabs to the completer satisfaction of all concerned.

Though granting the former premise, namely,- the practical impossibility of differentiating amongst the bacillary forms appearing in a "diagnostic" film,- there appeared to be no reasonable justification for continuing to allow such considerations to obstruct administration.

THE B. DIPHTHERIAE - its MICROSCOPICAL, STAINING, and CULTURAL CHARACTERS.

Before embarking on details, it were better perhaps to indicate somewhat briefly the multifarious appearances which the B. diphtheriae may from time to time present. In different text-books, bacteriological descriptions vary in detail but agree/

agree in principle.

Some such digest, as the following, may be claimed to reflect the accepted teaching of the most modern schools.

The B. diphtheriae is a slender rod presenting multiform appearances, being straight or slightly curved and varying from short rather sharply pointed rods to irregular forms with one or both ends swollen. It is usually about 3 u in length and from 0.5-0.8u in thickness. It takes up basic aniline dyes readily and is Gram positive. It stains more or less unevenly and intensely, so may present dotted, beaded, granular or solid forms. On culture, the organisms are at first fairly uniform in size and shape but involution forms appear in older cultures and the rods differ much in shape and appearance, club-shaped and bar forms being encountered. The bacillus evidently has very varying grades of virulence, down even to absence of pathogenic effects.

I3. Perhaps Osler, in his short account of the "Bacteria associated/

associated with the diphtheria bacillus", provides the best confirmation of the contention that the problem of differential diagnosis of the bacillary forms found in the throat and elsewhere is beset with difficulties.

In a description of the "Pseudo-Diphtheria Bacillus - B. Xerosis", he says:-

> "The Klebs-Löffler bacillus varies very much in its virulence and it exists in a form entirely devoid of pathogenic properties. This organism should not, however, be designated pseudo-diphtheria bacillus. The name should be confined to bacilli, which though resembling the diphtheria bacillus, differ from it not only by absence of virulence, but also by cultured peculiarities. A similar bacillus, showing however, certain cultural differences from the pseudo-diphtheria bacillus, has been repeatedly found in the conjunctival sac in health and disease (B. Xerosis). Organisms having the morphology of the diphtheria bacillus, but devoid of virulence, probably belonging to the group of pseudo-diphtheria and xerosis bacilli, have been described in human beings in association with a number of diseases, such as Egyptian dysentery (Kruse and Pasquale); they have been demonstrated upon the skin, in the crusts of variola pustules and in impetigo, in sputum, in pneumonia (Kruse, Ohlmacher), in gangrene of/

of the lung (Babès); in ulcerative endocarditis (Howard); in ascitic fluid (Harris); in pus from pyuria (Bergey); in ozoena (Wilder) and in tuberculosis (Schultz and Ehret)".

He might have added an association much more common than those enumerated, namely, in the otorrhoea of scarlet fever.

Microscopical examination of the cultures derived from such discharges has many times revealed to the writer bacillary forms in no way differing morphologically from the B. diphtheriae. In fact, this discovery suggested a series of investigations into the relationship between such bacillary presence in scarlatinal otorrhoea and the periodic disconcerting and troublesome outbreaks of diphtheria in scarlet fever wards.

It is of great moment to know whether, although such organisms are admittedly avirulent to the guinea-pig, their transference to the acute throats of recent admissions may not originate a true clinical diphtheria. Experience of this class of patient tends to confirm the possibility for, universal "swabbing" of every "scarlet" admission, with the resultant

rigorous/

rigorous exclusion and isolation of all "doubtfuls", in no way tended to lessen the number of "cross-infections".

A valid counter-argument of course is that one negative finding for B. diphtheriae does not entitle to presume its complete absence. It is conceivable, therefore, that the cause of these outbreaks is to be found in the recent admission whose "carrier" state has been missed. Such an explanation is unlikely, however, as it cannot readily be assumed that the condition would be missed in every instance.

These observations, made in a different field of investigation, serve to confirm the undesirability of dogmatism where diphtheroid organisms are in question.

Still another unmentioned association is that described by Ford Robertson and his co-workers who have obtained

I4 "from numerous cases of general paralysis of the insane cultures of a diphtheroid organism, which he considers is the chief agent in producing the condition of chronic intoxication underlying the disease. The organism has been obtained from various situations, including the central/

central nervous system, but it seems to flourish specially in the respiratory and alimentary tracts. It closely resembles the diphtheria bacillus, the morphological and cultural characters are indeed practically identical but the diphtheroid bacillus is non-pathogenic to the guinea-pig". I5. Osler further remarks that, "the clinical and bacteriological conceptions of diphtheria are at present not in full accord. On the one hand, there are cases of simple sore-throat which the bacteriologists, finding the Klebs-Löffler bacillus, call true diphtheria. On the other hand, cases of membranous, sloughing angina, diagnosed by the physician as diphtheroid, are called by the bacteriologists, in the absence of the Klebs-Loffler bacillus, pseudo-diphtheria or diphtheroid angina. The term diphtheroid may be used for the present to designate those forms in which the Klebs-Löffler bacillus is not present. Though usually milder, severe constitutional disturbance and even paralysis, may follow these so-called pseudo-diphtheritic processes".

It must appear to those with experience of diphtheria that the above is a laboured attempt to make distinction where there is no difference. It frequently happens that

a/

a patient, suffering from local and general symptoms and having all the characters of clinical diphtheria, cultures "negative" for as many days as are required to rid the throat of the false membrane. Is it to be wondered, that "clinical and bacteriological conceptions of diphtheria are not in full accord"? The explanation of the apparent inconsistency is simple. A consideration of the histological structure of the false membrane will demonstrate the mechanical impossibility, in given cases, of a "swab", lightly rubbed upon the surface, reaching the underlying diphtheria bacilli. The parts touched are swarming with pyogenic cocci, which, on culture by the bacteriologist, must give a "negative field". The cold scientific fact is that the particular "swab" submitted for examination is "negative". The cool conclusion, that the patient involved has no diphtheria organisms in or about the fauces, hence, cannot be suffering from diphtheria, is/

is unscientific and only serves to create a situation of professional embarrassment.

Scientific procedures cannot altogether supersede clinical observations. They must serve as valuable aids and, if accorded that function, but not relied on and acted upon slavishly, there will be no need to state such a contradiction in terms as, that - "though usually milder, severe constitutional disturbance, and even paralysis, may follow these so-called pseudo-diphtheritic processes"- and all for the want of a proper perspective and the commonsense balancing ofcontending forces. With the realisation that there need be no incompatibility between the bacteriologist's "negative" finding in an isolated throat swab and the practically undeniable presence ofa clinical diphtheria, scientific judgment need no longer be questioned nor clinical prescience discredited.

THE B. HOFMANN.

A/

A bacteriological survey would be incomplete without reference to the controversial organism described by Hofmann in I888 and known as Hofmann's bacillus.

I6. "It seems to be specially frequent in poorly nourished children of the lower classes. Cobbett found it I57 times in an examination of 692 persons examined, of whom 650 were not suffering from diphtheria. Boycott's statistics show that the time of its maximum seasonal prevalence precedes that of the diphtheria bacillus. To what extent, if any, it is responsible for pathological changes in the throat, must be considered a question which is not yet settled. Hewlett and Knight have found evidence that a true diphtheria bacillus may assume the characters of Hofmann's bacillus, but attempts to effect the transformation have met with negative results in the hands of other observers. The general opinion is that the two organisms are distinct species with comparatively easily distinguished characters".

I7. And again, Ker points out that it "is met with in many throats and its relation to the diphtheria bacillus has been the subject of much controversy. It is not pathogenic to guinea-pigs and it is a debated point/

point whether it is, or is not, responsible for any pathogenic throat conditions. The animal test adds considerably to the time which may have already been wasted in waiting for the result of a culture. Occasionally, a true B. diphtheriae may be non-virulent, and therefore even this physiological test is not entirely satisfactory. A negative result from a culture must be disregarded in the case of what otherwise shows the characteristics of a clinical diphtheria".

With so much dubiety regarding the nature of any given bacillus, it is satisfactory to be able to offer a specific vaccine as a ready and sure means of differentiation. From the proofs about to be offered, it may safely be concluded, that an organism which does not readily disappear under its influence is not the B. diphtheriae. With its exclusion, practical purposes are satisfied, for cumulative evidences point to the potential harmlessness of all the others.

DIPHTHERIA VACCINE - METHOD OF MANUFACTURE.

Having surveyed at some length the broad field of previous/

previous experience and practice bearing on the problem under review, it will now be opportune to proceed to the details of the subject-matter.

The vaccines employed in the treatment of the fifty cases were made in the following manner. Three, in all, were required to complete the series and each was obtained after the same fashion. Advantage was taken to inoculate the sloped surface of a solidified blood-serum tube with a "swab" from a patient who was known to be harbouring typical B. diphtheriae in the throat.

This was carried out before antidiphtheritic serum was administered, so that the vitality and virulence of the organisms would in no way be adversely affected. Search was made in the resulting growth for an isolated colony presenting the characteristic appearances of the organism. On being satisfied by microscopical examination that the colony selected was one of diphtheria bacilli a sub-culture was made and incubated for twenty-four hours at 37° C.

This/

This culture was emulsified in normal saline. The emulsion must be uniform, so that, if clumps are present the shaker or centrifuge must be used. A little of the living emulsion is withdrawn for the enumeration of the organisms which was done by Wright's method. The vaccine is then sterilised by heating in a water-bath at 60° C. for half-an-hour.

Sterilisation was tested by incubating some of the heated vaccine on a serum-tube for twenty-four hours. The concentration of the emulsion was usually such that I c.c. represented forty million organisms, and enough material was obtained from a single tube to ensure the production of 20-25 c.cs. of vaccine. Labour was not expended upon putting the vaccine up in ampoules. It was retained in a test-tube together with a few glass beads for agitating purposes. Contamination was prevented by the presence of a sterile rubber cap which, when a dose was

to/

to be given, was simply punctured by the needle attached to the hypodermic syringe and the desired amount withdrawn. The exposed surface of the cap was sterilised with iodine before and after puncture. Put up in such a form, the utmost simplicity in administration was secured and, if stored in a cool, dark place, the material was found to remain sterile and potent for many months.

VACCINE INFLUENCE UPON DIPHTHERIA BACILLI.

Not the least interesting part of the investigations was that dealing with the microscopical appearances presented by the cultured organisms at varying intervals after vaccine administration.

As will be gathered from the historical synopses of the cases to be subscribed later, the practice followed was to allow the specific antibacterial fluid to act for twenty-four hours. Throat swabs were then taken at daily intervals/

intervals for such time as appeared requisite.

After a considerable number of patients had been dealt with, it was realised that negativity for the B. diphtheriae was reached in various ways.

The morphological changes, observed in each instance, conformed to one or other of three types.

I. In a number of cases, a culture, characteristically positive twenty-four hours before vaccination, became completely negative twenty-four hours after vaccination. This, of course, was an ideal transformation and apparently depended upon immediate lethal influence of the vaccine constituents on the particular bacillary invasion concerned.

The following series of micro-photographs was taken from the actual films of Case 24 and well illustrates the type of immediate change under review.

Case 24 was given three courses of local throat treatment. The first and third consisted of a carbol-tannin paint, the second of a 2 per cent Chloramine T spray.

Each/

Each course lasted about a week butthe throat swabs remained positive.

I.

Fig. I shows a representative field of the film from the fourth positive, secured twenty-four hours before 4½ minims of diphtheria vaccine, representing ten million organisms, were administered.

It will be seen that the organisms have all the characters of typical B. diphtheriae. They are rod-shaped, slender, of considerable length, and possess well defined bipolarity.

2.

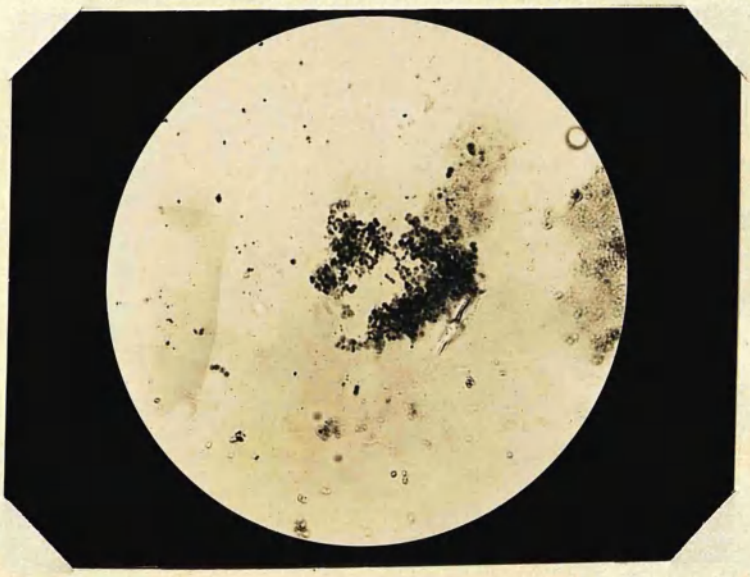
Fig. 2 is from a slide prepared with the cultured organisms removed from the throat twenty-four hours after vaccination. Although the organisms are clumped together forming a mass rather unsuitable for micro-photographic purposes the elements composing it are seen to be large cocci in no way resembling the rod-shaped bacilli depicted in Fig. I.

The film is negative for the B. diphtheriae.

3.

Fig. 3 shows the organisms appearing on cultivation of a throat swab taken forty-eight hours after vaccination. The organisms are staphylococci and M Tetragenus, ordinary bacterial inhabitants of the healthy throat.

The film is negative for the B. diphtheriae.



4.

Fig/

Fig. 4 illustrates the maintenance of negative appearances ninety-six hours after vaccination.

A throat swab, taken simultaneously with that from which this photograph was obtained, was sent to the City Bacteriologist who confirmed the negative character of the organisms presenting on cultivation.

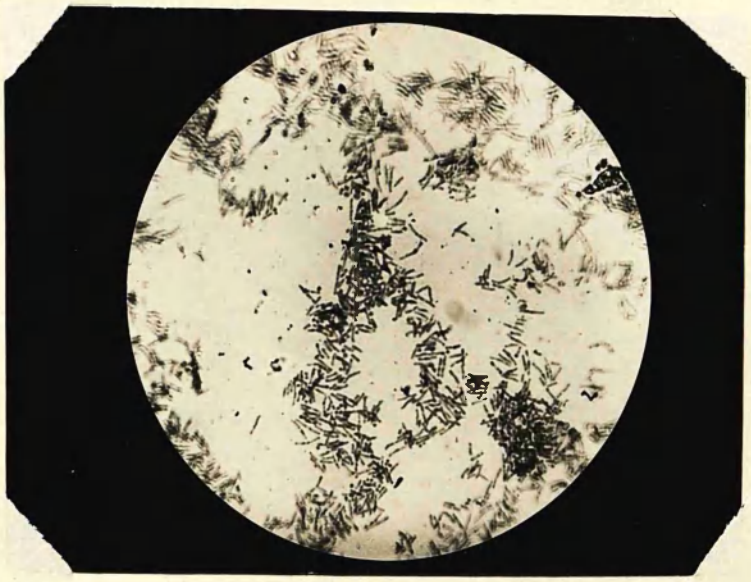
Of the fifty cases treated, thirteen conformed to this first type.

II. In many of the cases, the transition from positive to negative was accomplished in stages.

An organism, which before vaccination presented the microscopical characters of a healthy B. diphtheriae, in the presence of vaccine, became altered in certain well defined particulars.

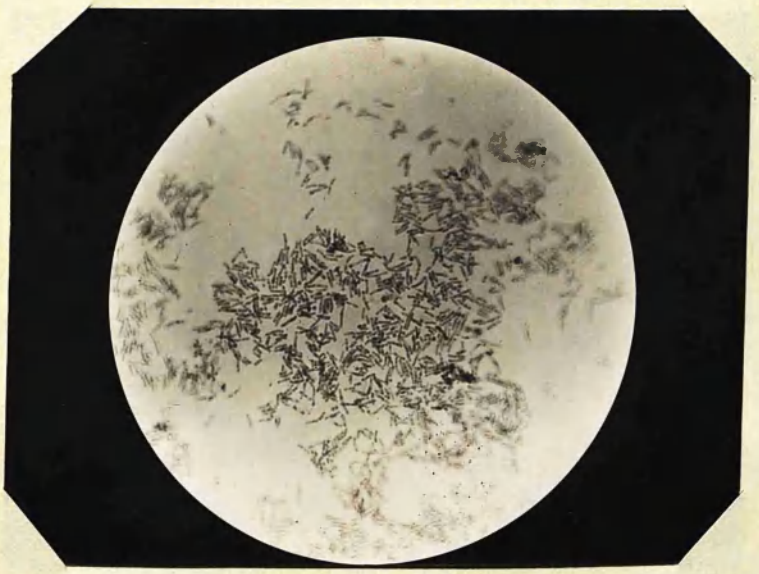
The capacity of the body protoplasm for taking up and retaining stains was reduced and the bipolar feature of the bacillus/

bacillus was less pronounced.



5.

Fig. 5 is of a film prepared from a throat swab taken twenty-four hours before administering vaccine to Case 36. It represents a typical field of diphtheria bacilli.



6.

Fig/

Fig. 6 depicts the changes which occurred after twenty-four hours contact with an amount of vaccine representing twenty million organisms. It will be seen that the above mentioned changes are plainly represented.

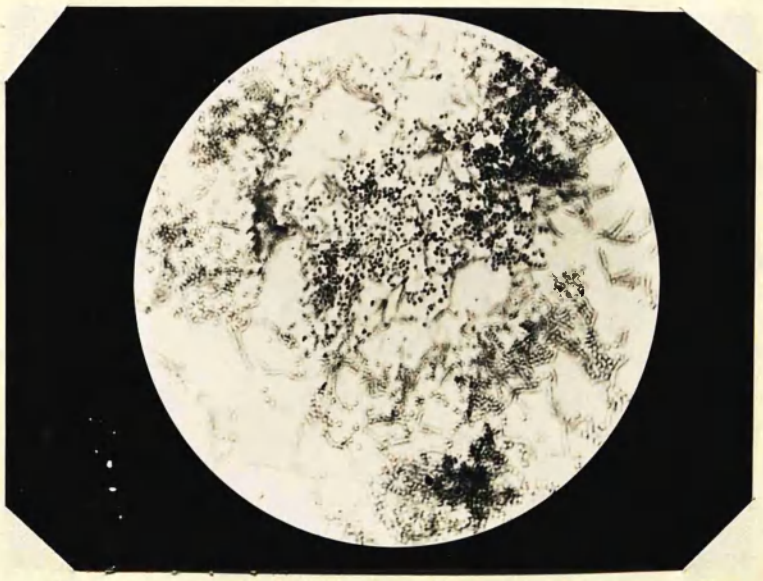
The organisms are attenuated and lack acute definition.

The bodies are unevenly and unequally stained. Here and there, actual vacuolation is indicated. Whereas in Fig. 5 the component organisms are wonderfully uniform and similar, now they are irregular and heterogeneous.

Bipolarity is not a striking feature. On the contrary, it is barely manifest, inasmuch as the rods contain, for the most part, varying numbers of darkly staining beads or granules.

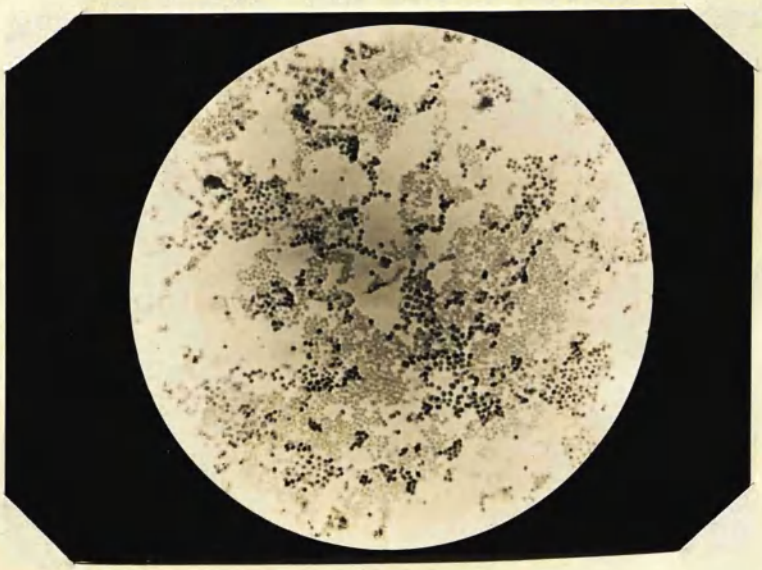
One is induced to describe such a field as consisting of Beaded degenerates or granular bacilli, whilst the term bacillary debris may aptly be applied to the appearances presenting/

presenting after further dissolution has taken place.



7.

Case 36 did not undergo the latter further change, for Fig. 7 represents the negative character of the throat swab taken twenty-four hours subsequent to that represented on Fig. 6.



8.

Fig/

Fig. 8 shows the persistent negative character of the faucial bacillary residents twenty-four days after vaccine was exhibited.

Twenty-four of the fifty cases dealt with progressed from positive to negative by stages representative of the types just described as beaded degenerates and bacillary debris.

III. In the remainder, metamorphosis occurred in a different manner.

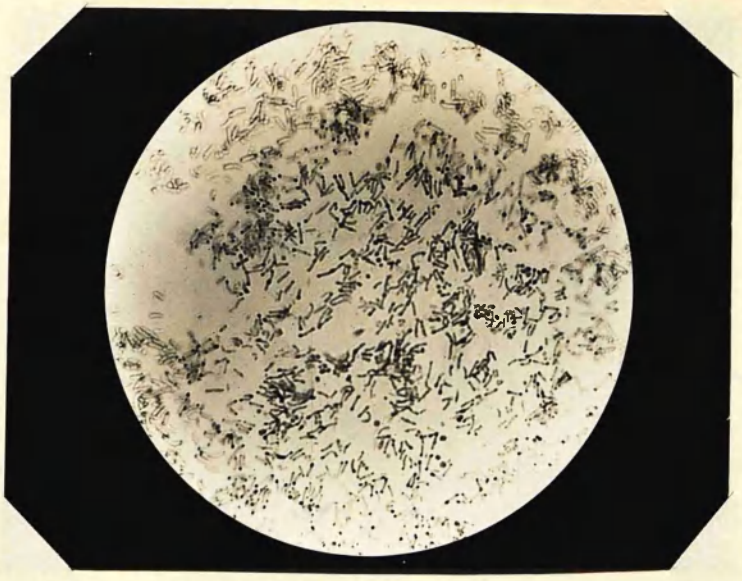
The transition was effected through various phases or modifications of diphtheroid change. Under treatment, the organisms showed a marked tendency to become rod-shaped; to be deeply, uniformly, and evenly stained: to be regular or irregular as to length, breadth, and shape and, apart from distribution over the field, so closely resembled B. Hofmann as to be microscopically indistinguishable therefrom. The transmutability (if the term be permitted in such a connection/

connection) of B. diphtheriae and B. Hofmann was described by Hewlett and Knight but later observers uniformly failed to substantiate the claim.

At the present time, the consensus of reputable opinion would recognise the two organisms as not only distinct but readily distinguishable.

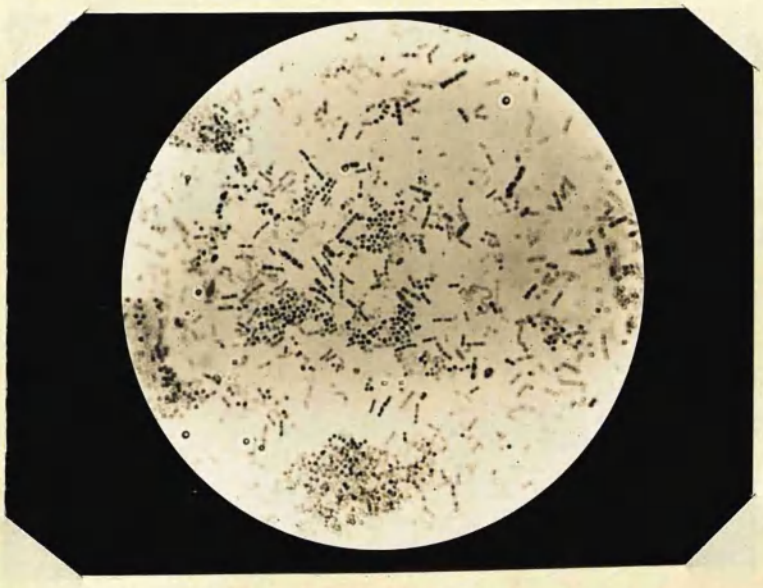
The writer is presently engaged on further study bearing upon this question but, although evidences have emerged which suggest that B, diphtheriae and B. Hofmann are correlatable, the investigations being incomplete, no opinion is offered meantime.

It is not proposed to burden the thesis by giving a separate series of photographs demonstrating the diphtheroid change, as Figs. 9 - I5 are sufficiently representative of the type and have the additional advantage of showing, in one and the same individual, degeneration conforming both to the beaded and diphtheroid varieties.



9.

Fig. 9 is of the film prepared twenty-four hours before injection of vaccine in Case I2, and affords a good idea of the characteristic features of healthy, well formed, virulent, diphtheria bacilli.



I0.

Fig/

Fig. IO clearly defines their altered appearance after a day's association with specific antibodies. The beaded degeneration is obvious. For the most part, four beads or granules appear in each attenuated rod. The body of the organism is shadowy and rarefied. The appearance is suggestive of short chains of streptococci.

Whether the quadruple incidence of granules results from juxtaposition and coincident shortening of two neighbouring bacilli or to protective focal concentration of body protoplasm is a matter for conjecture. Considered analogically with the endogenous sporulation propensities of other bacilli, it may be hazarded that the change depicted represents an anthrosporous counterpart.

This surmise is made with the twofold knowledge that the bipolarity of the B. diphtheriae has never been credited to spore-formation in the ordinary bacteriological acceptation of the term and that in any organismal growth powers/

powers of resistance to external influences may vary greatly among individual organisms.

None the less, the writer has been constantly struck by the peculiar persistence of the granular elements which certainly appear to have powers of endurance far in excess of those possessed by the body constituents proper.

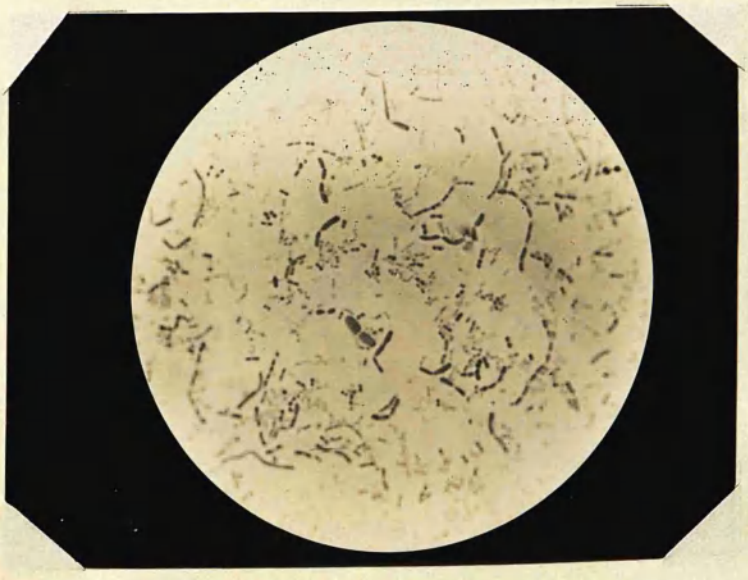
II.

Fig. II is comparable with Fig. IO but shows a further step in degeneration in that, for the most part, the granules have become approximated with the result that only the slightest/

slightest evidence of body protoplasm remains.

I2.

In Fig. I2 the granular phenomenon has disappeared so that short, stumpy, indeterminate, rods which offer but the merest suggestion of bipolarity are left.



I3.

Fig/

Fig. 13 is extraordinary in respect of the interposition of diphtheroid change in a series which otherwise preserved the type of granular degeneration.

The appearances depicted are similar to those possessed by such organisms as vanished through diphtheroid mutations. The combination of granular and diphtheroid changes occurring in this case was unique, since it was quite a feature of retrogression to remain true to type.

The theory is advanced that a double infection was here dealt with and that the individuals, representative of each invasion, behaved in the manner accredited to their different degrees of virulence or capacities for overcoming such inimical influences as altered pabulum and environment.

The organisms are strangely diplobacillary in form and vary much in size and shape.

Once more it is conjectural whether the appearances result from expansion into rod-forms of the poles of each bacillus

or/

13A.

or to fusion of the poles of contiguous bacilli. Although either interpretation would accountfor the distribution, careful examination of the relative dispositions suggests the former as the more likely.

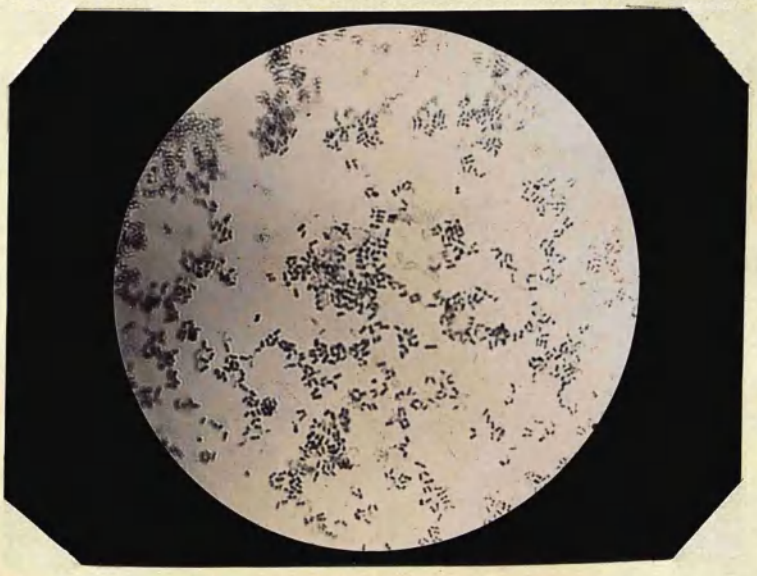
In most of the cases where this type of degeneracy occurred the succeeding stage was one where the organisms became uniformly and frankly rod-shaped. They showed no disposition to unite in chains and the transition seemed naturally to be brought about by segmentation of the antecedent rod-aggregations so that their uniform dispersal over the field was made possible. It is presupposed that at this stage all remnants of the body protoplasm disappear and that only the more resistant polar or granular elements remain.

Fig. I3Ashows still further attenuation of the bacilli. Both types of degeneracy are represented but in more exaggerated form. All evidence of beading has disappeared and/

and there remain organisms barely distinguishable from Hofmann's bacilli.

In many parts of the field it may be observed that the disposition in parallel twos is remarkably suggestive of the pseudo-diphtheria bacillus and that even the distinguishing "waist", insection, or unstained septum, is easily discernible.

Elsewhere over the field the later stages of diplo-bacillary dissolution, referred to under Fig. I3, may be noted. There is an inclination for the diploid feature to be lost as the organism assumes a definitely bacillary outline.



I4.

The remark is ventured that Fig. I4 would represent a stiff proposition in differential diagnosis to the microscopist.

The types presented might legitimately be designated coccoid, diplococcoid, pseudo-diphtheritic, but perhaps none would care to suggest that B. diphtheriae was represented nor had played a determining part in the production of the film.

I 5.

Fig. I5 typifies the absolutely negative appearances ultimately obtained.

The/

The film from which the print was taken was prepared several days after that of Fig. I4. The supply of serum-tubes was completely exhausted on the latter day so that the intimate involution changes occurring in the interval were not recorded.

However, there has been presented sufficient pictorial evidence to prove the vaccine's claim to specificity.

It is clearly capable of instituting well defined involution formation in the bodies of diphtheria bacilli with which it is brought into contact.

Many of the involution forms are comparable with those known to be producable by alteration in optimum-growing conditions.

Long continued incubation without subculture will provide involution forms of strange and fantastic proportions.

Doubtless, chemical influences, if carefully analysed, could be shown to initiate and perpetuate similar retro-

gressions/

retrogressions, as also might such factors as cultivation upon unsuitable media or incubation at other than a favourable temperature.

Certain it is that vaccine, which after all is organic in constitution since it contains the body plasm of diphtheria bacilli, is capable of initiating such involution formation in other members of the same family that total extermination results.

However much the foregoing may appear conjectural and beyond scientific determination, the records of the camera are incontrovertible and provide that ocular demonstration which proverbially is more believable than volumes.

VACCINE ADMINISTRATION IN FIFTY CONSECUTIVE CASES.

The series of cases about to be considered was consecutive. They occurred in the ordinary course of practice in one of the City of Glasgow Isolation Hospitals. They were in no way selected. Each one, as it appeared, was taken up and treated to a successful issue.

During vaccine administration, no accessory treatments, general or local, were at any time employed. Although a considerably greater number is on record now, those showing more immediate good results have not been substituted for such in the present series as proved refractory, since much useful information was gleaned from dealings with the latter.

The writer had come to the conclusion, that persistence of the B. diphtheriae, in the throats of convalescents from diphtheria, might be caused by one or other or any combination of the following four conditions.

I. Innate lack of resistance on the part of the hosts - mainly contributed to by the presence of a concurrent resistance-lowering condition, such as pneumonia.

II. Spread by continuity of tissue - causing infection of any of the accessory nasal or pharyngeal passages.

III. Severity of the original local involvement.

IV. Individual tolerance or natural predisposition - "carriers"/

"carriers", or those with "bad fever histories".

Bearing these premises always in mind, especial care was taken to search for and note the presence of any such likely determining factor.

For the purpose of elucidating the possibilities, it will be advisable to classify the cases under the customary text-book categories.

Taking, then, the somewhat arbitrary designations of "mild", "moderate", and "severe", it is found that sixteen (one-third) fall into the first classification, two into the second, and thirty-two (practically two-thirds) into the third.

"MILD" CASES.

Of the "mild" cases, the histories, in brief, are as follow. (The figures in the margin represent the numbers of the cases in the series).

Case IO. A member of the staff, nursing in a diphtheria ward. She, admittedly, was recognised early as, "sore-throat", under such circumstances, was by order made immediately notifiable. Serum/

Serum was promptly given and the invasion checked.

Cases I3 & 26. Both soldiers who were recognised "carriers". They had been discovered during a routine bacteriological examination of the inmates of a barracks where clinical diphtheria had manifested itself. Neither had objective signs nor subjective symptoms.

Case 26 developed otorrhoea - he must, therefore, have sustained a middle-ear infection with the B. diphtheriae.

Case I4. Patient suffered from scarlet fever. The ward in which he was resident became "crossed" with diphtheria. He was the only "positive" discovered, so was concluded to have been a "carrier" and the cause of the diphtheria outbreak.

Case 28. Was admitted as a "bacteriological" diphtheria. She had been a contact of another member of her family already in hospital with diphtheria. She, consequently, had her throat swab cultured and it proved "positive". It was reasonable to assume that she had been a "carrier" and

the/

the probable source of her brother's illness.

Case 49. Patient had two sisters in hospital. The Sanitary authorities, in the course of their routine examination of the contacts in the home, discovered her with a "positive culture". She, equally, might have been a "carrier" and the source of her sisters' illnesses.

Put briefly, of the sixteen cases, one (Case IO) was mild, because of peculiarly favourable circumstances allowing of early diagnosis and treatment. It may therefore be left out of account.

Five were almost certainly "carriers".

The remainder (ten) comprised the following.

Case 9. Poorly nourished and pale. Eczema intertrigo of groins, buttocks, perineum. Head retraction. Peevishness, on interference, which caused the suspicion of meningitis. Marked general pulmonary catarrh with fine râles - broncho-pneumonic in type.

Case II. Had an acute bronchitis which developed, three days after admission, into a lobar pneumonia.

Case 21. No apparent disability on admission but, twenty-five days thereafter, she developed scarlet fever.

Case 25. Definitely mild - no apparent disability.

Case 29. Healthy and the subject of a mild attack. After nine days' residence, however, she developed scarlet fever of a septic type and was most dangerously ill for three weeks. Had left otorrhoea for three weeks.

Case 32. Little on the throat. Had a bad cough, bronchial in origin. Presumably, the main involvement in this case was of the lower respiratory tract - a diphtheritic broncho-pneumonic catarrh. There was a large patch of active ringworm on the scalp.

Case 39. Poorly nourished and obviously neglected, as was evidenced by the presence of profuse impetigo contagiosa over the occipital region.

Case 40. Definitely mild - no apparent disability.

Case 43. Healthy patient. Throat condition mild. There was an accompanying German Measles. Possibly, attention might not have/

have been paid to this child's throat, had not the roseolar rash caused alarm.

Case 45. Poorly nourished patient - pale and anaemic: almost marasmic in habit.

TABLE A.

Table showing the Classification of the Fifteen "Mild" cases:-

I.		II.		III.	
Case 9.	Broncho-pneumonia and Eczema.	Case 13.	Carrier.	Case 25.	Mild.
" 11.	Lobar pneumonia	" 26	"	" 40	do.
" 21.	Scarlet fever	" 14	"		
" 29.	do.	" 28	"		
" 32	Broncho-pneumonia Ringworm.	" 49			
" 39	Malnutrition Impetigo contagiosa.	"			
" 43	German measles				
" 45	Marasmus				

It will be seen (Table A) that, of the fifteen "mild" cases who developed late persistence of the organism, in two only/

only (Cases 25 and 40) was there no predetermining factor discoverable and, even they may have had an undiscoverable invasion of the antrum of Highmore or Eustachian tube.

Of the remainder, eight had complicating diseases (enumerated in Table A) and five showed individual tolerance or were "carriers".

In other words, 86 per cent satisfied one or other of the original premises.

"MODERATE" CASES.

Of the two "moderate" cases, it might be said that:-

Case 5. Had congested throat with considerable patching of both tonsils. She was dismissed on the forty-first day of illness, having given two "negative" cultures. Her brother complained of sore throat on the fourth day of her return home and was admitted to hospital three days thereafter. He had not been confined to bed. Her culture was taken and it was proved she was a "carrier". She was readmitted to hospital eleven/

eleven days subsequent to dismissal. She had no complaints and was in splendid health. No more serum was given.

This patient provided suitable "clinical material" for the carrying out of the following controlled experiments.

She had two courses of formalin treatment (as previously outlined) to the throat. Forty days were lost using this method.

Three doses in all of vaccine were then given and two "negatives" obtained by the eleventh day.

She was not dismissed for twenty-five days more, when she was still "negative", as confirmed by the City Bacteriologist.

This child provided a good instance of a diphtheria convalescent causing a "return case" on dismissal. Meikle's contention of avirulence, referred to above, did not find confirmation here.

It will be seen, that advantage was taken of the unusual circumstances/

circumstances to give local treatment an extended trial, to follow its failure with vaccine,(thereby testing the one method against the other and in the same patient), and to detain her for as long as possible to discover if the organisms made their reappearance. Also, after the "negatives" were obtained, no local throat treatment was employed nor was she segregated nor protected in any way, but lived in a receiving ward, liable at all times to the incursion of acute and virulent cases. If she had had any predisposition to reinfection, every facility was offered.

With a view to ensuring that the application of local antiseptics should not be denied a fair trial, two courses were carried out. They proved unavailing even after the expiry of forty days. The administration of vaccine, however, succeeded in removing the offenders in eleven days. To avoid the possible argument, that such removal was no more than a lucky chance, the child was retained in the ward for three and a half weeks, but there was no return.

Such/

Such a test, of course, was unusually and unnecessarily severe, as no person, outwith a hospital ward, was ever likely to be the contact of such concentrated infection as was that child. The circumstance, that she resisted faucial reinvasion, may with certainty be credited to the provision of artificial specific antibodies. It is claimed for the case that it provided a very complete test for the efficiency of the vaccine.

Case 47. Well developed and well nourished child but, although only two years of age, had already suffered from measles and scarlet fever. With such a history, it might logically be concluded that her natural immunity to the fevers was negligible.

Of the two "moderate" cases, therefore, represented in the series, it may be summarised that, persistence in one, was conduced to by individual tolerance, in the other by natural predisposition.

These observations, it will be noted, were still in conformity with the original hypotheses.

The third category of "severe" cases contains by far the greatest/

greatest proportion of the total number, namely, thirty-two. All were justly considered to have had "severe" initial lesions and consequently satisfied the third of the four favouring etiological factors.

With a view to conveying a general impression of the usual features manifested, the histories, only in so far as they illustrate the theory in point, are appended in brief. Such cases as are favoured with more elaborate descriptions point a particular moral or illustrate features of more than passing interest.

A more considered commentary and summing up, together with a classification table, will be subscribed at the end of the historical synopses.

"SEVERE" CASES.

Case I. Bad faucial with accompanying bilateral anterior cervical adenopathy. Child was the subject of a concurrent bilateral blepharitis (non-diphtheritic).

Case 2. Bad faucial withaccompanying glandular enlargement. Marked seborrhoea of the scalp.

Case 3. Bad faucial. Acute bronchitis.

Case 4. Bad faucial. The subject of a tabes mesenterica.

This patient was resident in the hospital for two hundred and eight days. She had two courses of formalin treatment to the throat, extending over twenty-six days, but without result. This was followed by a six days course of Tinct. Iodi. (B.P.) applications which likewise proved unavailing. Every attempt was made to build up the general health with special feeding and tonics. This presented difficulty on account of the capricious appetite, and the tendency any attempt at full diet, much less over-feeding, had to produce sickness, vomiting, diarrhoea, and abdominal distress.

In all, ten doses of vaccine were given, extending over a period of fifty-two days. A swab, taken on the forty-fourth day of treatment, was submitted to the City Bacteriologist for the "virulence test" which was reported negative/

negative ten days thereafter, during which time, the ninth and tenth doses had been given. Fifty-eight days before the vaccine was commenced, the organism had proved virulent to the guinea-pig,- a condition which likewise obtained two days before treatment was instituted.

The conclusion drawn was that, at some time during the subsequent forty-six days, the organism, although persistently reported "positive" became avirulent. Also, it was assumed that, had the physiological test been applied after each dose of vaccine, the avirulent character of the organism might have been discovered much earlier. However, although ten doses were given, the latter two at least were unnecessary. As to just how many of the remaining eight were required to produce avirulence remains unknown. As the result of such an experience, and in the event of a comparable case occurring, the precaution would have been taken to have earlier "virulence" tests applied to the persisting organism. In this particular patient, then, who/

who was by far the most refractory of the series, the vaccine must at all events be credited with the production of avirulence, if not the customary total disappearance of the tonsillar bacillary residents. This case, moreover, was the first to receive vaccine. It will be granted that the experience therewith was sufficiently disheartening to have spelled disaster to the project, had not more stimulating evidences been present elsewhere. Fortunately, the similar treatment of four other cases was commenced almost simultaneously. The early and complete realisation of one's object withthem, prompted a perseverance with the first which, under different circumstances, would have been lacking. As a result, the facts detailed emerged, and with them the valuable information, that an originally malign organism was at any rate convertible into a benign. Other notable features of the case were, that she was not only given the benefits of the most accredited local applications/

applications over an extended period, as recommended by Ker but, in addition, she was dieted and drugged in a manner, sufficiently special to have satisfied the demands of an Osler. Failure of such approved and intensive treatments coupled with the fact that she was the subject of a well established scrofulous manifestation, served to provide the most unfavourable clinical material available. The result obtained may be conceded as satisfying very exacting conditions.

Case 6. Laryngeal diphtheria. Tracheotomy performed. On the sixth day of residence, acute bronchitis developed. On the thirty-sixth day, left internal strabismus appeared.

Case 7. Bad faucial accompanied by bilateral anterior cervical adenopathy. 20,000 units serum given - which large dose was indicative of the serious nature of the local involvement. On the fourth day, palatal paralysis manifested itself.

Case 8. Bad faucial.

Case I2. Bad faucial and laryngeal: required steam.

Colour poor: child extremely toxic. Had been ill for fourteen days.

This patient required eight doses of vaccine extending over thirty days. Presumably, her resistance had been lowered to vanishing point during the time before admission - a fortnight, in which the toxin was free to pervade her system. In spite of an earlier resolve to prevent repeated vaccinations, in this instance also, the administrations were persisted with and no recourse was made to the physiological test, for information regarding the toxic influence (upon an animal) of the particular bacillus in question. It would have been interesting to discover whether a few injections produced avirulence and, if so, whether the remainder was required to bring about complete dispersal. The point would have been well worth investigating but, in this particular, as throughout, the work was performed/

performed under war-time disabilities. Laboratory materials were at a premium and, almost invariably, were unprocurable when most needed.

Unfortunately, organismal states are precisely limited in time, and it is not possible to maintain them for short periods, much less indefinitely, whilst awaiting the overdue arrival or tardy manufacture of the more complex differentiating media. Guinea-pigs were all along most difficult to procure and many times were unobtainable.

Case 5. Bad faucial. Marked anterior cervical adenopathy. IO,000 units serum given. Had five doses of vaccine and required twenty-five days to negative. Was only twenty-one months old, had contracted diphtheria in late convalescence from measles, was consequently vulnerable to bacillary invasion, and would have little natural resistance to combat persistency.

Case I6. Laryngeal, faucial, nasal. Put in steam-tent. Distinct cardiac (irregular) irregularity.

Case I7. Bad faucial. Marked anterior cervical adenopathy.

Case I8. Bad faucial. Sharply ill: pale: toxic. Ill for seven days. On twenty-third day, developed left middle-ear infection with otorrhoea which continued for twenty-eight days when vaccine was given. On fourth day thereafter, otorrhoea had ceased and, by sixth day, the throat also was clear.

Case I9. Laryngeal. Put in steam-tent.

On fifth day, left otorrhoea commenced. The discharge teemed with B. diphtheriae. Those were true B. diphtheriae and not diphtheroids, as shown by the sugar reactions. The otorrhoea ceased on the day following an injection of a dose of vaccine containing ten million organisms.

Case 20. Patient had scarlet fever and an extremely bad accompanying faucial diphtheria with considerable bilateral anterior cervical adenitis. 30,000 units of serum were given during first three days of residence. On twenty-second day, left otorrhoea appeared and, on twenty-fifth day, right otorrhoea/

otorrhoea. These persisted for nearly nine weeks but were absent for a week before vaccination commenced. Although she required five doses, this was not surprising, considering her original condition and the double middle-ear infection from bilaterial Eustachian tube contamination. Eighteen days were required to "negative" her throat swab.

In this connection, an original theory, for the persistence of the B. diphtheriae in the convalescent throat, is offered.

The generally accepted inefficiency of local antiseptic throat applications is assumed to be due to Eustachian tube infection constituting a constant source of faucial reinfection.

Antiseptics, as locally applied, even although their use in lethal concentration were practicable, can do no more than inhibit the growth of or sterilise the organisms met with on the parts reached. They cannot penetrate such/

such an accessory structure as the tube just mentioned and hence need not be entrusted with a mission of complete bacillary extermination.

The point, as to whether or not Eustachian tube infection occurs, need not be laboured.

Apart from the corroboration which is afforded from an analogous observation, namely, that many laryngeal diphtherias which have persistently cultured "negative" for weeks, ultimately become "positive" for a throat swab, (thereby demonstrating the spread of causal organisms from upper respiratory tract to fauces - Cases 30 & 33), there is clear proof of the contention in the fact that the otorrhoea of diphtheria is of specific origin and terminable by the exhibition of a specific antibacterial-containing vaccine.

The organisms isolated in the cases treated (Cases I8 & I9) were not diphtheroids nor pseudo-diphtheria bacilli (which are/

are not infrequently present in otorrhoea from varying causes), as their true nature was verified by the application of the sugar tests and the physiological determinant.

Case 22. Tonsillar and nasal. Thin, puny child. 10,000 units serum.

Case 23. Tonsillar and laryngeal. Pulse feeble. Tracheotomy performed, two hours after admission. 8,000 units serum repeated on the second day. Right otorrhoea appeared on thirty-first day and persisted for a week.

Case 24. Laryngeal. Voice husky, almost inaudible. Dry, "throaty", ineffectual cough. Put in steam-tent.

On thirty-third day, bilateral loss of accommodation present.

Case 27. Tonsillar and laryngeal. General broncho-pneumonic catarrh with urgent cough. Developed middle-ear infection with otorrhoea on forty-first day. Required four doses vaccine extending over twenty-four days.

Case 30. Laryngeal. Colour poor, cyanosis marked.

Tracheotomy/

Tracheotomy performed within a few hours of admission. Culture "positive" from mucus in wound, "negative" from fauces for thirty-six days, when B. diphtheriae appeared and persisted until dispersed by vaccine.

Case 31. Tonsillar and laryngeal. Colour poor. General broncho-pneumonic catarrh. Tracheotomy performed.

Case 33. Laryngeal.

The diphtheria organisms did not appear in the throat for fifteen days but remained for twenty-seven days when they were removed in one day with a dose of vaccine containing twenty million organisms.

Case 34. Laryngeal. Very croupy. Put in a steam-tent.

Case 35. Laryngeal. Croupy. Put in steam-tent.

Case 36. Tonsillar and laryngeal. Croupy. Put in steam-tent.

Case 37. Extensive patching of both tonsils. Child toxic, having been ill for five days. Active ringworm on scalp.

Case 38. Bad faucial. Local lesion spread after admission, necessitating additional serum on the second day.

Case 41. Laryngeal. Poorly nourished: pale: cyanotic.

Tracheotomy performed shortly after admission.

This boy had been, for the preceding two years, an out-patient at a general infirmary where he was treated for the late effects of an infantile paralysis.

In this connection, the following account of a rare condition is perhaps worthy of mention. In conformity with practice, the tracheotomy-tube was removed on the third day. As obstruction recurred, it was returned eleven days thereafter. Such recurrence of obstruction was singular but probably resulted from cicatrisation of the tracheal wound causing such a deformity of the trachea as to reduce effectually its normal patency. The tube was removed in forty-eight hours. After a further nine days, tracheotomy had again to be resorted to on account of the extreme respiratory embarrassment. Even after twenty days, he was unable to do without his tube. The wound, therefore, was freely opened up and the/

the trachea examined with a view to the possibility of there being a "tag" of tracheal tissue acting as a ball-valve. No such condition was found. The cicatricial tissue, however, was dissected away from the trachea. On the tenth day, the tube was finally dispensed with. To all appearance, then, this case provided an example of the rare condition of a patient who had developed the so called "tube habit". He brooked no interference with the "brooch" for, on its removal, obstructive phenomena were immediately induced. This was demonstrated by the experiment of withdrawing it very carefully in his sleep. He was not incommoded but, on waking and realising its absence, he started up in a fit of terror which brought on the appearances of an actual respiratory obstruction only relieved by replacement of the tube.

Case 42. Tonsillar. Serious involvement. 12,000 units serum given. Albuminuria present for fifteen days. This patient required five doses of vaccine and took thirty days to clear.

Case 44. Bad Faucial. I2,000 units serum given.

Ill for five days before admission, and, as a result, more than usually toxic.

Case 46. Tonsillar. I2,000 units serum.

Ill for four days, during which time there had been serious toxic absorption.

Case 48. Laryngeal. General broncho-pneumonic catarrh.

Tracheotomy performed shortly after admission.

Case 50. Bad faucial. Marked involvement. 8,000 units serum, followed on succeeding day by I6,000 units as membrane showed signs of extension.

TABLE B.

Table showing the Classification of Thirty-two cases with "Severe" initial lesions:-

Tonsillar	2
Faucial	I3
Tonsillar and Nasal	I
Faucial and Laryngeal	I
Laryngeal and Tracheal	9
Four Tracheotomies	
Tonsillar and Laryngeal	5
Two Tracheotomies	
Faucial, Nasal, Laryngeal	I

All/

All laryngeal cases of diphtheria were classified as "severe", in spite of the fact that the toxin absorption from the laryngeal and tracheal mucous membranes is not only less than from the nasal but even from the faucial.

The seriousness of the obstructive type of the disease is not only in the immediate risk of tracheotomy but in the very usual, in fact, the almost invariable accompanying bronchial and pulmonary catarrh of undoubted diphtheritic origin. This disability, taken in conjunction with the vitality-lowering toxaemia of diphtheria, exerts a crippling and devitalising influence requiring many weeks of convalescence to overcome.

There is ample proof that the bronchitis, broncho-pneumonic catarrh or actual broncho-pneumonia (so constantly associated with croupous involvement of the upper respiratory tract) are caused by the B. diphtheriae. This fact is readily appreciated by observing the remarkable manner in/

in which these respective conditions clear up under the influence of serum especially when given in successive doses. Much is to be gained by pushing the serumuntil the respirations and temperature fall.

The cases, then, presenting "severe" lesions, afforded additional proof of the truthfulness of the original contentions for, with but rare exceptions, all possessed predetermining complications.

Thus, of the thirty-two individuals involved, twelve had some form of broncho-pneumonic disease, three had "accessory passage" infection (two with otorrhoea and one with rhinorrhoea), whilst four had a double infection of lungs and middle-ear.

Of the remaining thirteen cases, eleven had very serious membranous involvement of the fauces, whilst two presented more than usually severe tonsillar lesions.

In all the "severe" cases, it may be taken that,

by/

by reason of the co-existence of the favouring factors, the ground had been well prepared for diphtheritic bacillary persistence. Had a prognosis been demanded, it might well have been based upon the desiderata suggested, as in no case would the forecast have been erroneous.

FACTORS PRESUMPTIVELY CONTRIBUTORY TO THE PRODUCTION OF "POSITIVE THROATS".

Now that a broad classification of cases, under the headings of "mild", "moderate", and "severe", has been completed and conclusions drawn therefrom, some further considerations emerge.

Since there may be various factors contributing to the production and maintenance of a morbid state, careful note was taken and record kept of many circumstances which were thought likely to have etiological bearing upon bacillary persistence.

Attention was accordingly directed to questions of sex/

sex and age, the pre-existence of albuminuria, the brand of serum given, the infectious fever history of the patient, and the day of disease on which serum was administered.

Regarding the etiology of diphtheria itself, it is recognised that, in the first ten years of life, sex exercises a negligible influence. After that age, for many well defined reasons, domestic and otherwise, females naturally fall more ready victims to the disease.

The series of carriers of the B. diphtheriae, presently under review, was made up from twenty-two males and twenty-eight females. Taken in conjunction with the age incidence, it will be seen that such a proportion is not at variance with that maintaining in the disease itself.

No proof, then, is forthcoming that sex, "per se", exerts any particular predetermining influence.

With regard to the question of age, it was not found

that persistence of the B. diphtheriae in convalescence was liable to affect disproportionately those at one time of life more than at another.

TABLE C.

Table showing the Age-incidence of a series of Fifty cases:-

AGE.	1 - 5	6 - 11	12 - 16	20 - 25	36.
NUMBER.	30	13	3	3	1

Diphtheria is peculiarly a disease of the first ten years of life and veryespecially of the first five. The period from infancy to twelve years claims the majority of cases. It will be seen from Table C that 60 per cent of the patients requiring vaccine were under six years of age and that 86 per cent were under twelve.

As the individuals enumerated in the last two columns consisted of two members of the staff, nursing diphtheria, and/

and two soldiers, previously referred to, it may be taken that their infections were chance ones, and that, had their circumstances and environment been less incriminating, they would have escaped. If, for the reasons indicated, they be left out of account, there remain but 6 per cent who were over twelve.

Here also, it can only be concluded that the question of age does not appear.

Again, in a well marked case of diphtheria, albuminuria is a frequent symptom.

TABLE D.

Table showing the Number of patients who had Albuminuria:-

Albuminuria. Lasting 3 - 22 days	None.	Urine unobtained. Under two years of age.
I6	27	7.

I8. "In averagely severe diphtheria the proportion of patients/

patients with this symptom is about 30 or 40 per cent: but when the epidemic is benign in character the percentage may be very much less."

It will be seen (Table D) that although 32 per cent suffered from toxic interference with the nervous mechanism of the kidney, the fact of seven (fourteen per cent) being in doubt vitiates the significance of the statistics.

Except in so far as albuminuria is admittedly indicative of a "severe" initial lesion, (thereby fulfilling the third of the postulates), it is apparent that pre-existing toxic nephritis had little, if any, influence in determining late bacillary persistence.

Further, an interesting point was to discover if the particular brand of serum administered governed in any measure the future conduct of the B. diphtheriae in each instance.

Strangely/

Strangely enough, examination of the records reveals the coincidence that twenty-five were treated with Burrough and Wellcome's brand, twenty-five with Parke Davis.

The German make of serum, much in use in pre-war times, was unobtainable, hence no observation can be made upon it here.

It is to be regretfully admitted that experience of all the sera then available proved the German brand least provocative of serum troubles and most rapid and effective in its local and general actions.

In these respects it stood alone and consequently had established itself in high favour with antidiphtheritic serum therapists.

The spirit of inquiry would have been stimulated and gratified by any disclosure of its unfavourable comparison in the present connection.

However, it may justifiably be concluded that, for all practical/

practical purposes, serum variation plays no appreciable part in the causation of "positive" throats.

A noteworthy point for consideration was that of previous infectious disease, more especially as it related to involvement of the respiratory tract and lungs.

TABLE E.

Table showing the Infectious Fever History of Fifty cases:-

Measles.	Whooping Cough.	Measles and Whooping-Cough
I8	4	I5

In very many of the cases the diphtheritic attack had followed closely a previous measles or whooping-cough. In fact, in no inconsiderable number, the former infection was a convalescent sequel of the latter.

The very lack of resistance which predisposed to the subsequent infection presumably militated against the early dispersal of the invading bacilli.

It would appear that mucous membrane, damaged by the inflammations/

inflammations accompanying such fevers as measles and whooping-cough, especially when further violated by diphtheritic toxin absorption, forms a very suitable locale for the perpetuation of B. diphtheriae.

Table E. indicates that eighteen had had measles, four whooping-cough, and fifteen both measles and whooping-cough. In other words, 74 per cent of the patients (practically three-fourths) had been, in the more or less immediate past, the subjects of just such damaging influences as would produce indifference to the presence of an organism which readily assumes saprophytic propensities.

Inasmuch as these findings are corroborative of those which have been fully indicated previously, they need not now be elaborated further than to reiterate that preceding or concurrent respiratory tract disease appears a truly potent factor in the production of "positivity".

Lastly, consideration was given to the day of disease

on/

on which serum was administered.

The following table shows very strikingly the advantage to be gained by the early exhibition of serum in the treatment of diphtheria.

I9. "Table showing the Mortality of Diphtheria according to the day on which Serum was first injected in 2,496 consecutive cases".

Day of Illness.	Patients.	Deaths.	Percentage of Mortality.
First	90	2	2.22
Second	6II	20	3.27
Third	707	38	5.37
Fourth	504	45	8.92
Fifth	276	26	9.42
Sixth	I22	I2	9.83
Seventh	I04	I4	I3.46
Later	82	I4	I7.07
Total	2,496	I7I	6.85

Patients who are saturated with toxin, absorbed for three or more days, cannot be expected to have many antibodies (antitoxic or antibacterial) intheir blood-streams. Although the antitoxic properties of the latter are artificially enriched by the addition of antitoxin, no attempt is made to provide antibacterial substances. The very natural corollary that the longer the initial delay, the greater the liability to subsequent "positivity", might be anticipated, and the following table (Table F) proves its accuracy.

TABLE F.

Table showing the Day on which Serum was first injected in Fifty consecutive cases.

Day of Illness.	Patients.	Day of Illness.	Patients.
First	2	Sixth	6
Second	I4	Eighth	I
Third	4	Twelfth	I
Fourth	5	Fourteenth	2
Fifth	I4	Twenty-first	I

Thirty-four patients did not receive serum until the third day or later.

This represents a big percentage of the total and is a point worth taking into account in estimating a prognosis or if called upon to indicate roughly the length of time a given individual is likely to be incapacitated or isolated. It ought to be possible to make such estimates with reasonable accuracy. At least they will have to be attempted as, in the future, they will be demanded in the interests of commercial economics. If it can be demonstrated that, after a given day of untreated illness, there is a greater tendency to late persistence of the causal organisms, both the patient and parties interested in him might be warned of his probable protracted residence.

It is relatively uncommon to find patients, who have not secured the benefits of serum till the fifth day of illness, ridding themselves of the tonsillar infection within the normal period. Moreover, it is noteworthy that, generally speaking, the originally neglected lesion is, as

one/

one might anticipate, the forerunner of the case which is refractory even to vaccine therapy. Possibly every treatment known to modern medicine is more potent in its action, more certain in its cure, and more permanent in its efficacy the earlier its application. Here, there is no exception to the golden rule that prevention is better than cure and time the principal determinant.

Of the six cases which took longer than a fortnight to clear up with vaccine treatment, one only (Case 15) had been given serum on the supposed second day of illness. Of the others, three came under observation on the fifth day, one on the sixth, and one as late as the twelfth.

As with Ker's table, (p.107)it is to be explained that the history of the case, as given by the mother, was accepted. Since the majority of admissions was drawn from the poorest class population of the "East End", in whom the earliest signs of disease are not usually recognised or heeded, it is/

is extremely probable that most of the illnesses were of longer duration than was alleged. In any case, 60 per cent who became carriers were not given serum before the fourth day of invasion. In fact, twenty-five or exactly 50 per cent, did not reach hospital until the fifth or later day of illness.

It may be safely concluded, therefore, that length of untreated illness bears a direct relationship to probability of "carrying".

Until a considerable number of cases had been observed, the possibility of simple coincidence bulked largely in any interpretation to be put upon the apparent cures. It was necessary, therefore, to produce some evidence which would negative such a conclusion.

In the first instance, the vaccine was reserved for such patients as had been in residence for unduly prolonged periods. This was done deliberately, as it had been proved that/

that most "positive" throats cleared up sooner or later without interference. The successful application of the vaccine during the earlier periods of convalescence, might certainly have been inconclusive, since it was open to argument that the organisms were disappearing in any case and that it was fallacious to credit the vaccine with their removal.

In order clearly to demonstrate that such a view was untenable, opportunity was taken to commence treatment at very varying periods pf residence. A glance at Table G. will make this clear.

TABLE G.

Week of Residence.	Cases.	Week of Residence.	Cases.
Third	3	Tenth	3
Fourth	7	Eleventh	2
Fifth	3	Twelfth	I
Sixth	5	Thirteenth	3
Seventh	2	Fifteenth	2
Eighth	IO	Sixteenth	3
Ninth	5	Twentieth	I

It could not readily be assumed that in fifty consecutive/

consecutive cases, treated over periods ranging from the third to the twentieth weeks, mere coincidence offered sufficien explanation. In the majority of cases, the diphtheria organism disappears from the throat in the course of the first ten days or thereby, although, in a minority, it shows a tendency to reappear about the beginning of the fourth week. Normally, however, by the sixth week, when "dismissal" swabs are due, there is no sign of bipolar bacillary forms in the resulting films. The patient, therefore, can be dismissed free from infection. The converse may be claimed to be equally true, namely, that all cases showing a persistence of the organisms up to and including the sixth week are potential carriers and unlikely to become "negative" for an indefinite period.

Thirty-two of the cases (64 per cent) were not interfered with until the seventh week or later. As it had been found that it was in just such resistant cases that the older methods failed/

failed, it was felt that they provided the severest test for vaccine treatment. Since many of them had already been given full courses of the most accredited preparations, formaldehyde etc., without effect, resort was finally made to the vaccine with results that justified its use.

In support of this claim, one example may be quoted -

CASE 10. Nurse-, aet 24, admitted 2.1.17.

Patient was well nourished. Tongue slightly furred. Throat congested, no patching. Slight bilateral anterior cervical adenitis.

Heart, lungs, kidneys - normal.

12.1.17. Complaint of nausea and anorexia.
Sodii Bicarb. and Liq. Pancreat mixture t.i.d.a.c.

23.1.17 Above mixture discontinued.

26.1.17. Allowed to sit up in bed.

30.1.17. Allowed up in clothes.

3.2.17. Culture positive.

12.2.17. Culture positive.

16.2.17. Culture positive.

23.2.17. Culture positive.

Throat treated lightly with the B.P.Tinct.Iodi.

27. 2. 17. Throat treatment discontinued.

1.3.17. Culture negative.

3.3.17. Culture positive.

8.3.17. Culture positive.

Throat swabbed t.i.d. with 2 per cent Chloramine T.

10.3.17. Above treatment discontinued.

11.3.17. Culture positive.

4½ minims Diphtheria Vaccine - 10 millions injected.

13.3.17. Culture negative.

14. 3. 17. Culture negative.

15.3.17. Dismissed free of infection.

Many similar cases of histories might be recorded but, as they are practically reflections of the one given, their repetition is unnecessary.

On being satisfied that the vaccine possessed potency under the conditions of experiment already outlined, it was thought wise to test its influence in early cases. The possibility of a given medium having a very different influence upon an organism at the third week and at the twentieth was not overlooked. It was granted that legitimate objection to the methods could be based on such an hypothesis as

that/

the twenty-weeks-old saprophyte might very well succumb, whilst the three-weeks-old parasite might be quite unaffected. Opportunity was accordingly taken to vaccinate thirteen cases during the third, fourth, and fifth weeks of illness. (Vide Table G. p.112). This was the more readily undertaken as there was curiosity to learn if the antibacterial influence might not be evanescent. It was felt that two or even three consecutive "negative" swabs did not preclude the possibility of an earlier or later return of the bacilli.

In the ordinary course of hospital practice, it was not possible to retain patients already resident for weeks and months, in order to investigate this problem. When, however, those in early convalescence were dealt with, such a disability did not exist.

The following detailed report will suffice to instance the vaccine's reasonable durability of action:

CASE 36. Isa - , aet 3, admitted 11.4.17.

Patient was well nourished. Tongue furred. Throat congested, patch on right tonsil. Heart - normal. Lungs - mild general, catarrh.

Child was croupy and required steam.

12.4.17. Culture positive.

16.4.17. Steam discontinued.

28.4.17. Culture positive.

29.4.17. 9 minims Diphtheria Vaccine = 20 millions injected,

1.5.17. Film showed no typical bipolar staining bacilli but mere bacillary debris and beaded degenerates.

2.5.17. Culture negative.

3.5.17. Culture negative.

4.5.17. Allowed to sit up in bed,

11.5.17. Allowed up in clothes.

12.5.17. Culture negative.

24.5.17. Culture negative.

26.5.17. Dismissed free of infection.

In this particular case, the vaccine was given on the eighteenth day of residence and the throat swab was found to remain "negative" twenty-four days thereafter. Except in a few minor and unimportant details, this case reflects the remaining twelve met with, but the question of permanency of action will be alluded to later.

Early vaccination proved of great value in two others where, for reasons hereafter set forth, it was desirable that early dismissal should be secured.

CASE 9. Mary -, aet 1, admitted 13.2.17.

Patient was poorly nourished; very pale; "ailing" for past three weeks. Artificial dermatitis on back of chest due to poulticing. Dermatitis of groins, buttocks, perineum. Child had a double internal strabismus. There was considerable head retraction, accompanied by peevishness on interference. Her crying was almost continuous and there was a "cerebral" character about it.

Tongue very furred; throat congested, clean.

Heart - sounds week and indeterminate.

Lungs - catarrh general over back of left chest.

There was diarrhoea.

15.2.17. Culture positive.

Lumbar puncture proved "negative" for the meningococcus.

10.3.17. Culture positive.

11.3.17. Child unusually fretful, peevish and noisy. As there was no peace night nor day for the other patients in the ward, it was dicided to give vaccine

early in the hope of ensuring dismissal.

13½ minims Diphtheria Vaccine = 30 millions injected.

13.3.17. Culture negative.

14.3.17. Culture negative.

15.3.17. Dismissed free of infection.

It is clear that the hope entertained was justified as one medium dose negatived the "positivity" and made her dismissal possible within four days.

The other case bearing on this aspect of the subject may be cited as it typifies many to be met with in fever practice. The result obtained was not only satisfactory in itself but especially in that it afforded a happy augury for future situations of a like kind.

CASE 11. Patrick - , aet 1 8/12., admitted 25/2/17.

Patient was very poorly nourished. Tongue furred. Throat congested, clean. Cough somewhat urgent. Heart - sounds accelerated but of fairly good quality. Lungs - acute bronchitis general in both lungs.

26.2.17. Culture positive.

28.2.17. T. 102.8°F: P. 164; R. 46. Lobar pneumonia,

right chest, lowest lobe.

1.3.17. T. 104°F. Cough severe. Pneumonic spread to middle and upper lobes.

2.3.17. T. 104.8°F; P. 170; R.62. No change.

4.3.17. During past 24 hours, temperature dropped by crisis to 98.4°F.; P. 156; R.48. Probably a pseudo-crisis.

5.3.17. Temperature rising.

9.3.17. For past five days continued fever ranging between 101°F. and 102°F.

10.3.17. On this, the sixth day after pseudo-crisis and the eleventh day of the disease the temperature declined. (99.2°F.)

11.3.17. T. 97.2°F; P. 145; R.44.

17.3.17. Culture positive.

23.3.17. Culture positive.

25.3.17. As the mother of the patient was dissatisfied with his progress and was convinced that if she could treat him at home with "poulticing and the run of the house," (which had apparently included liberal quantities of butcher meat), it was decided to use vaccine against the possibility of meeting this wish.

$4\frac{1}{2}$ minims Diphtheria Vaccine = 10 millions injected.

27.3.17. Culture negative.

28.3.17. Culture negative.

29.3.17. Dismissed free pf infection.

The knowledge that a satisfactory conclusion might with reasonable certainty be reached on the fourth day after injection (as obtained in the case just quoted), relieved the previous feeling of impotence in the face of popular clamour, discontent, and troublesomeness.

Further considerations suggesting themselves for discussion are those of dosage and number of injections of Vaccine which it was found necessary to administer to ensure success.

TABLE H.

Table showing the Dosage given in the series of cases.

Millions of Organisms.	Cases.	Millions of Organisms.	Cases.
10	11	50	2
20	17	60	1
30	13	200	2
40	4		

It was naturally felt that the smaller the dose the more readily would it recommend itself, since four and a half drops/

drops of fluid need not alarm even a very youthful patient, especially as no pain is caused when it is injected into the soft tissues in the interscapular region.

The situation indicated was found in practice to be quite the most suitable for, the skin is less sensitive than in most other situations and further, the fact of being able to work behind an infant adds not a little to the simplicity of the operation as it can be completed before the child is conscious of any unusual interference.

In the majority of cases, a very few injections were found requisite to effect the purpose.

TABLE J.

Table showing the number of doses of Vaccine given.

Doses of Vaccine	Number	Doses of Vaccine	Number
One - - - - - -	24	Five - - - - -	3
Two - - - - -	15	Seven -.- - -	1
Three - - - - -	5	Eight - - - - -	1
Four - - - - -	1		

Table J shows that, by vaccinating every fourth day, 88 per cent of the cases, having received at most three doses, could have been dismissed on the tenth day.

The next Table (Table K) shows in more detailed fashion the number of days after vaccination during which the throat swabs remained "negative" in each of the fifty cases comprising the series.

TABLE K.

Table showing the Number of Days during which the Throat Swabs remained "Negative" after Vaccination.

Number of Days.	Cases.	Number of Days.	Cases.
Two	13	Ten	1
Three	7	Twelve	1
Four	8	Thirteen	2
Five	5	Fifteen	1
Six	1	Seventeen	1
Seven	2	Eighteen	3
Eight	1	Twenty-four	1
Nine	1	Twenty-seven	2

On account of the exigencies of the situation (cp.p.116) nearly three fourths of the patients were dismissed within seven days of thecompletion of treatment as it was found impossible to retain a larger number for observation purposes. Nevertheless, fully one-fourth remained for from eight to twenty-seven days without manifesting renewed "positivity" or sustaining re-infection.

It may be claimed that such a proportion justified the

vaccine's claim to reasonable efficiency.

Still another point on which information was sought and collected was that concerning the length of time occupied in obtaining the results.

It is obvious that all practicable therapeutic procedures should be conservative of time and very especially during war when, if ever, there is truth in the adage, "time means money". It is also clear that, in the language of the work-shop, given an appliance which is a "time-saver", the "output"must be facilitated, and "maintenance" costs reduced. The economics of the subject will, later, be dealt with separately. For the present, a glance at the table (Table L) will show that the time consumed in effecting the object varied within considerable limits, namely, one to thirty days.

The single case (Case 4) which remained apparently unaffected after thirty days is purposely excluded for reasons fully outlined in the text above (p.83).

TABLE L.

Table showing the Number of Days taken to "Negative" the Throat Swabs in the series of cases.

Days.	Cases.	Days.	Cases.	Days.	Cases.
One	19	Eight	2	Fifteen	1
Two	3	Nine	2		
Three	1	Eleven	1	Twenty-four	1
Four	1	Thirteen	1	Twenty-five	1
Five	7	Fourteen	1		
Six	3			Thirty	2
Seven	3			Forty-four	1
First Week.		Second Week.		Third week and later.	

Examination of the figures reveals these facts.

In thirty-seven cases (74 per cent), or practically three-fourths of the total, the object was attained within one week, forty-four (88 per cent) or, adding the one which required fifteen days as being sufficiently comparable to warrant inclusion, forty-five (90 per cent) required two weeks, whilst only four (8 per cent) took longer.

It may fairly be accepted, therefore, that, so far as the time factor is concerned, the vaccine treatment of "positive throats" is unassailable by comparison with any of the other means advocated.

VACCINE EFFECTS - PULSE, RESPIRATIONS, TEMPERATURE, SKIN.

Finally, there fall to be recorded any untoward effects which were noted on the vaccinated patients as evidenced by examination of the pulse and respiratory rates and the temperature charts.

In most cases, vaccination was performed when the morning ward visit was paid between 11 a.m. and 12 noon. The radial pulse was taken hourly for about forty-eight hours from 9 a.m. and the rate charted graphically as in fig. I. (Overleaf)

In order to obtain such charts as those depicted, it is essential that the pulse rate be recorded for two or three hours before the vaccine is administered. If this precaution be not taken, the first upward tendency will be lost as the normal pulse rate of the particular individual will not be known. In the case of infants, (and it has been shown that they form the bulk of diphtheritic victims), wrong conclusions will be drawn unless extreme care is exercised - for the very slightest psychical disturbance causes quite disproportionate

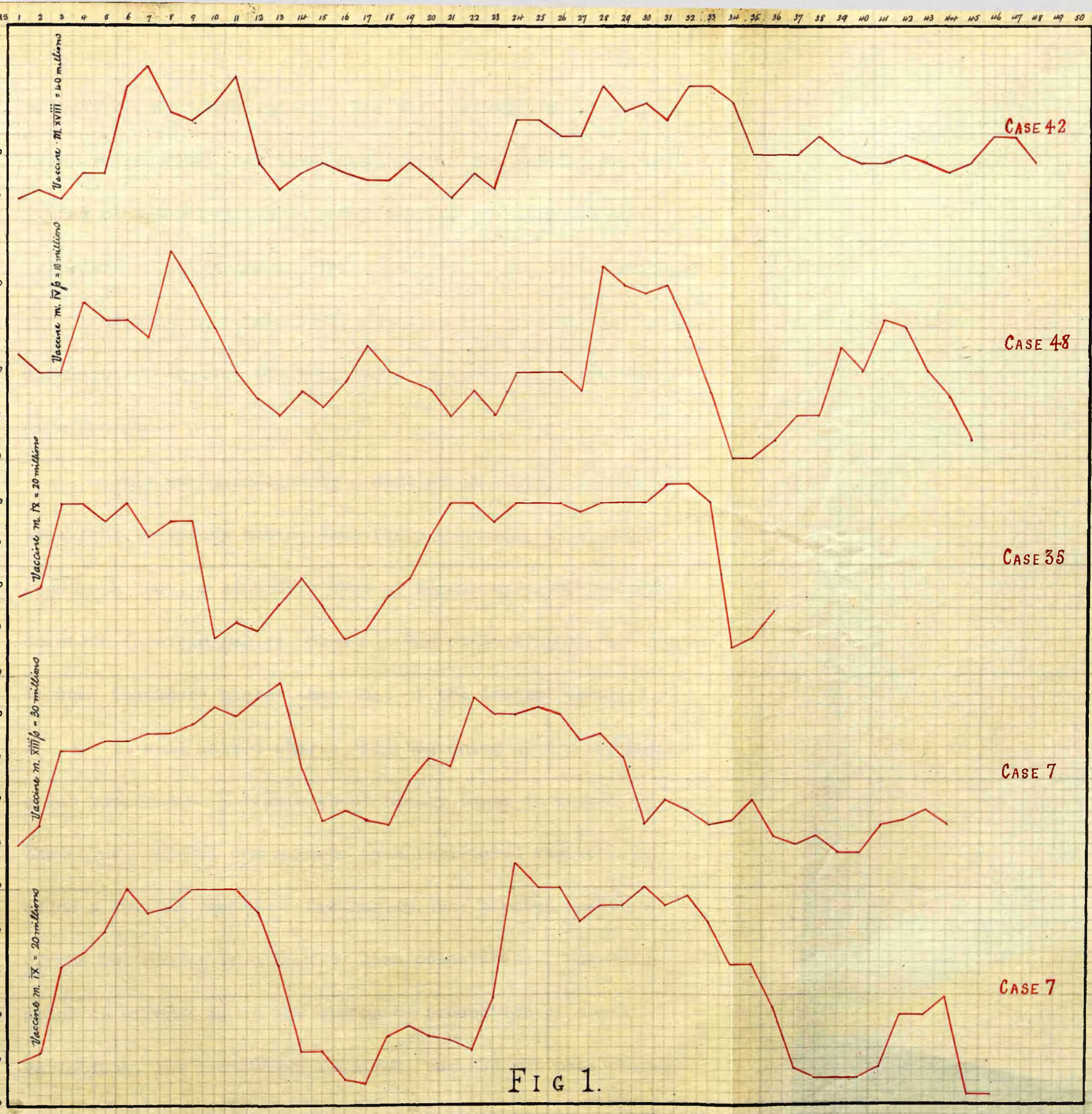

Hours 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50
Vaccine m. XVIII = 40 million
Case 42
Vaccine m. IVβ = 10 million
Case 48
Vaccine m. IX = 20 million
Case 35
Vaccine m. XIIIβ = 30 million
Case 7
Vaccine m. IX = 20 million
Case 7

Fig 1.

effects on heart and pulse. The mere glimpse of a "preparation-tray" has been known to vitiate results and any crying or undue excitement makes records of pulse-rates valueless. The sequence of cardiac events was very constant.

Usually in a few hours, one to six, there was an initial acceleration lasting for from three to seventeen hours (average, nine hours).

This was succeeded by a wave of depression extending over four to twenty hours, when there occurred, about the twentieth hour, a secondary wave of acceleration of variable duration (average, twelve hours). The crest of this latter was in some instances higher than that of the initial wave.

In well marked charts, the beginning of the primary crest represented a figure about twenty beats in excess of the normal, whilst the maximum rate registered frequently added a further twenty. Ordinarily, the topmost registers of the two crests were more or less comparable. No scientific proof is offered as to the method of production of these variations, the mechanisms involved, nor the intimate changes which doubtless predicate them. It is tentatively suggested

that they are explicable by the haematological disturbances which are believed to be engendered by the introduction into the blood-stream of any vaccine. In fact, the curative properties, undoubtedly possessed by vaccines, are believed to be due to the production in the serum of so called "phases." Jack declares that, "upon the injection of a suitable dose of vaccine there follow (1) a brief period ("negative phase") in which the opsonic content of the serum is lowered, the existing opsonin being partially used up in sensitising the organisms, and (2) a longer period ("positive phase") in which opsonins are produced in increased quantity, in response to the stimulus. This increased production is maintained for from ten days to a fortnight or more ("high tide of immunity"), after which the opsonic production declines to the normal. A second injection during the declining phase produces a repetition of the process, and thus maintains the opsonic content of the serum above the normal level, thereby rendering the organisms of the particular infection more amenable to phagocytosis."

It may be that the variations in pulse-rate follow the evolution of these "phases", so that the wave of depression might be represented as coinciding with the "negative phase", whilst the succeeding wave of acceleration would synchronise with the onset of the "positive phase" or period of "High tide of immunity". If such conjecture be true, the primary crest would require to be credited to psychical disturbance following the interference accompanying the administration.

Whether or not such a theory is plausible, the facts remain and are recorded as clinical observations.

With respect to the respiratory rate, it was mostly unaffected as any increase recorded did not exceed a few per minute.

Pyrexia was exceptional and was noted on but three occasions. An individual temperature of 100.2°F. was once recorded in a patient of less than a year old. As the child concerned was liable, for no very well defined reason, to sudden "forks" of temperature the above reading may be dis-

counted or credited to mere coincidence.

No local reaction at the site of injection was ever produced nor was there, at any time, complaint of pain or stiffness on the part of any patient.

Patients were kept in bed for convenience of observation and to prevent vitiation of pulse-rates by exertion. As no cause for anxiety ever manifested itself, it can be safely claimed that confinement to bed is an unnecessary precaution. There would therefore appear to be no contra-indication to treating a "carrier" as an out-patient and permitting his return home out of reach of medical observation. Such a practice would represent a considerable advance on the present-day methods which necessitate the indiscriminate removal of many to the Isolation Hospital and their treatment there as fully established cases of clinical diphtheria. Apart from the undoubted hardship imposed on individuals, considered from the monetary standpoint alone, the latter procedure is indefensible.

ADMINISTRATIVE AND ECONOMIC CONSIDERATIONS.

In conclusion, it will be interesting to judge of the advantages of practising vaccine therapy in diphtheria "positives" from the administrative and economic points of view.

To a large extent, success in hospital administration centres round the problem of early dismissal of patients. This applies especially to fevers where, from the very nature of things, peculiar difficulties are more liable to arise than elsewhere.

When it is realised that patients are compelled by law to leave their homes and be isolated for long periods without opportunity of seeing their relatives and friends, it will be conceded that the situation is a delicate one demanding tactful handling alike by the medical and nursing staffs.

The scanty reports available to visitors, either through the medium of an inquiry office or daily bulletins in the press, more particularly where young children are

concerned, not uncommonly appear to create a feeling of uncertainty in the minds of parents. Could they be permitted to see their children, as can be done in all General Hospitals, anxiety would be allayed and easy relationships between staff and friends more readily maintained. Under the circumstances, however, even such a small privilege cannot be granted, so that it need not be wondered at if, after seven, eight, nine or more weeks, an attitude of open hostility is engendered in the parties interested and charges of insincerity and even neglect levelled at administrative heads.

It may be recollected that, in the introduction to this thesis, it was stated that it was in the hope of relieving just such situations as those indicated that this investigation was undertaken.

As to how far the effort has been realised must be left to impersonal judgment based upon the facts and figures set forth above.

The economic aspect of the subject is scarcely separable from the administrative, but, for convenience of statement, an

arbitrary distinction will be made and some figures which may be of interest presented.

In pre-war days, outlay, civic or national, was not subject to overmuch scrutiny. Mere expense in administration, unless flagrantly excessive, was of surprisingly little moment provided a reasonably obvious return in efficiency was demonstrable. With the advent of war, however, and the consequent revision of ideas regarding expenditure, retrenchment became a password, and any measure likely to check the rapidly mounting maintenance costs, was welcomed. In such a department of Civic activity as that devoted to Public Health, there is no monetary return for the large sums expended. Whereas in most other departments, economies could be effected in many ways, Public Health was afforded no relief. It must be obvious, then, that any means which can be shown to ease the burden of costs is acceptable and worthy of general employment.

Vaccine treatment of the "positive throat" in diphtheria when judged by this money-saving standard, will be seen to be of considerable value. As most of the cases comprising the

series were taken from two wards in the Hospital, the following comparative estimates of averages were drawn from figures of similar series in the same wards.

Fifty cases, as recorded in the Ward Journals, were taken at random from each ward for the years 1915-1916. The average number of days' residence was found to be fifty-three and fifty-five respectively or, of the total one hundred cases, fifty-four. On the other hand, the average days' residence of fifty patients, taken indiscriminately from the "non-carrier" population of the same wards in which the "positives" were being treated, worked out at forty-three, whilst the figure for the vaccine treated was seventy-one. The average of the latter two series will be seen to be fifty-seven, or three days more than for the first two series. The difference is to be accounted for by the inclusion, amongst the present series of "carriers", of an unusual number of extremely "long" cases. It must be rare indeed to have a patient resident for two hundred and eight days or to have, in a short series, seven others whose average stay in hospital extended to sixteen and a half weeks.

In any case, it may be concluded that, on an average, each person who became a "carrier" lost exactly four weeks as compared with one in whom the bacilli showed no tendency to persist.

From the mass of evidence offered, it appears that this loss is unnecessary and need not be countenanced for the future.

Unfortunately, on account of difficulties surrounding the inquiry, the percentage-figure of "carriers" to"non - carriers" amongst diphtheria patients could not be ascertained. Had such a figure been obtainable, a simple calculation would have shewn the total number of days lost per annum from a preventable cause, by the aggregate diphtheria admissions.

The following figures relate to the year 1913-14, that is, the financial period immediately preceding the outbreak of war. They are the last which are readily available, as reports in the elaborate and detailed form then obtaining have not since been published. With the realisation that the purchasing power of the sovereign is now about 8/3d, it will

be granted that the call for economy is urgent and insistent. It appears that the average cost per patient during the year indicated amounted to £10. 2. 6.: that the average daily cost per patient was 4/2.7°: that the average cost of treatment per patient was £9.12. 9.4 and that the average cost of bed per year was £77. 2. 4.8. In the light of present values, these figures will convey their own meaning and it need only be stated that, the present average daily cost per patient being fully 8/-, there is cause for satisfaction in the use of an expedient which reduces the average residence, of even a proportion of the total admissions, by a period of twenty-eight days.

A simple calculation reveals the fact that every diptheria patient who becomes a "carrier" costs the chargeable authority, in food alone, £1. 15/- more than one who is dismissed at the end of the present average period of residence.

During the year under review ('13-14), 1996 cases of diptheria and membranous croup were registered. The average

daily residence of all these patients was 47.9. There appears to be no real reason for such a lengthy residence, for with the exception of a small minority of patients who fall victims to paralyses and late complications, sufferers from diptheria are convalescent and able to get about from the middle of the fourth week. With the exception of those indicated, might not all the others be dismissed after a maximum residence of five weeks ? So far as the writer's experience has gone, nearly four years' observation of diptheritic patients not only confirms the possibility but suggests the advisability of a less protracted hospital residence for this disease. Until vaccine had been used, it was not possible to break custom in this regard as, in many, the means were not available to justify it, but with the introduction of the specific the only disability was removed.

If the term of residence of 1996 patients were reduced from an average of 47.9 to one of 35, the number of days gained would be 25748.4.

Taking into consideration food only, at the very

moderate cost of 1/3d per head per day, this would represent a saving of over £1609, and if all Local Authorities were to encourage Vaccination as a means of rendering "positive throats" "negative", the saving in expense, and labour, and hospital accommodation would be incalculable.

However, it is unnecessary to multiply such figures of costs, as sufficient light has been thrown upon this aspect of the subject to justify the economic soundness of vaccine therapy in the condition forming the text of this thesis.

ADDENDA.

1. The efficacy of the Vaccine in the prophylaxis of diphtheria, amongst medical attendants, nurses and contacts, is a question which can only be referred to here. It may be said, however, that the measure is on trial, and indications point to its undoubted value in such a connection.

2. Since the completion of the fifty cases above set forth, twenty-five further successes have been put on record.

CONCLUSIONS.

1. Local antiseptic throat applications are unreliable cures for the "carrier" and the "positive throat."

2. B. Hofmann should be definitely dissociated from B. Diphtheriae.

3. Diphtheria vaccine produces well defined degeneracy in morphological appearance of the cultured organism followed by its complete dispersal from the locality invaded.

4. In the past, the diphtheria "carrier" has been subjected to hospital residence for weeks, perhaps months, which now prove to have been easily avoidable.

5. Diphtheria vaccine is effective in the treatment of the "positive throat" of diphtheria convalescents and its use is administratively and economically sound.

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