The second phase of the outbreak was dealt with in general on the lines advocated by Fulton, Taylor, Wells, and Wilson (1941), with the exception that combined active and passive immunization was confined in the main to Schick-positive reactors. Four cases developed after this procedure; two were Schick-positives (Cases 15 and 18) who had received 500 units of antitoxin and 0.3 ml. of A.P.T. 14 and 21 days, respectively, before the onset of their illness, and the other two (Cases 16 and 17) were Schick-negative children. In view of the fact that four cases went down in the 24 hours intervening between Schick testing and reading it is clear that it is inadvisable to wait even 24 hours for Schick-test results before carrying out immunizing measures in the face of virulent infection. Furthermore, four of the cases were Schick-negative reactors. The repeat swabbing and boosting doses to Schick-negatives before readmission after the Easter holidays were carried out as additional safety measures. A difference of opinion exists as to the value of general swabbing, and it is true that most of the carriers gave only one positive result, although a few were more persistent.

In this district, where the average incidence of diphtheria is low and the diphtheria carrier is almost non-existent, it has been the policy to swab close contacts and to take measures to restrict their movements when positive. In an episode such as this it would be difficult to ignore the possible danger to others from unknown carriers of virulent organisms, and universal swabbing, with full recognition of its limitations, should be employed. It should, however, be completed in the shortest possible time so that all infected children, whether carriers or cases, may be excluded without delay.

It is clear from this experience that even a highly immunized community as judged by present-day standards is not entirely safe against a very virulent type of organism. It is also clear that immunization is of limited value unless it is maintained by boosting doses at regular intervals during the whole of school life. Opinions will differ as to how much of this work is necessary or practicable in order to reach the desired end. Parents do not take kindly to over-frequent injections for their children, and after infancy the frequency of sharp reactions with A.P.T. has a bad propaganda value for the whole scheme of immunization. Even T.A.F. is not without its quota of discomfort. The Schick test is not reliable enough to justify the omission of immunizing injections in negative cases, but serves a useful purpose in measuring the conversion rate of various batches of antigen. In the present state of our knowledge it is suggested that the normal immunizing course in infancy should be followed by a boosting dose of selected antigen every three years irrespective of Schick-test readings. The antigen selected and the dose given will be a matter of individual choice.

Summary

An outbreak of diphtheria is described which occurred in a day school where 94% of the children had a history of previous immunization and 80% were Schick-negative.

The necessity for repeated doses of antigen during the whole of school life is emphasized. The interval suggested between doses is three years.

The limited value of the Schick test as a measure of immunity is pointed out.

I should like to express my gratitude to Dr. Stone, of the E.M.S. Laboratory, Epsom, for her most valuable help in carrying out the bacteriological work, and to the medical officers of health of adjoining districts—Dr. Ellis, Dr. Ive, Dr. Johns, and Dr. MacIntyre—for their enthusiastic co-operation.

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FAUCIAL DIPHTHERIA AMONG ARMY PERSONNEL IN BELGIUM, 1945

AN ANALYSIS OF 122 CASES

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The purpose of this paper is to discuss certain aspects of the diagnosis and management of diphtheria in circumstances a little different from those usually obtaining in civil life. It was known before the invasion of Europe that diphtheria was prevalent in German-occupied Belgium and Holland, and it was recognized that when this part of the Continent was reached the disease might become a major medical problem. Consequently, compulsory lectures and demonstrations were arranged for medical officers of adjacent units. Prompt administration of serum was stressed and the admission to hospital of doubtful cases was encouraged. It followed that a very large number of patients who in normal circumstances would never have got beyond the stage of ambulant treatment were admitted to hospital for a brief period and had a thorough bacteriological investigation of their throats.

The Investigation

Bacteriology.—The absence of facilities for testing the virulence of organisms limited the scope of the investigation, and the bacteriological diagnosis has depended upon assessments from the point of view of morphology, cultural characteristics, and biochemical reactions of the organisms. The following bacteriological technique was employed: Preliminary throat swabs were plated on: (1) tellurite plates (Hoyle's modification)—it is better to avoid human blood in this preparation as it is less inhibitory to organisms other than those of diphtheria; (2) blood-agar plates, 5% blood; (3) Loeffler slopes. A smear was stained with methylene blue and examined for Vincent's organisms. No attempt was made to diagnose diphtheria on the direct smears. The next day a combined smear was made from the Loeffler slope and the blood-agar plate and stained with Albert's stain. The blood-agar was also examined for haemolytic streptococci and the Hoyle plates were inspected for growth. If the slide was positive a diagnosis of morphological diphtheria was made and the result was immediately sent to the ward. The Loeffler slope which showed a morphological diphtheria bacillus was retained. If there was no growth on tellurite in 48 hours the Loeffler slope was subcultured to another tellurite plate. The following day the Hoyle plates were examined. Colonies were studied macroscopically and microscopically. All those showing a rod form were subcultured to a medium which was found to have an advantage over a Loeffler slope.

The medium consisted of 10% serum (animal sera were better than human); 100 ml. of agar; 0.50 ml. of neutral red as supplied for MacConkey's medium; and 1% saccharose. The last three were heated together until the agar was melted, and on cooling to 45.5° C. the serum was added and it was then poured into Petri dishes. This medium was found to be of more value than subculturing back to Loeffler slopes, for the following reasons: (1) Colonies on this medium could be viewed and easily manipulated. (2) Frequently when using Loeffler slopes cocci were found as a contaminant on subculturing

from Hoyle plates. (3) Single colonies could be picked off with ease and put into saccharose Hiss serum water. (4) With experience the saccharose and non-saccharose fermenters could be differentiated immediately. (5) The morphology, altered by growth on tellurite, was immediately restored on the serum-saccharose medium. The growth on the above medium was then subcultured to glucose and starch serum-water media. Haemolysis was studied by subculturing on to 5% blood-agar plates.

The diagnosis as to type was based on: colonial appearances on tellurite plates; morphological appearance of organisms from a serum-sucrose medium; sugar reactions; presence or otherwise of haemolysis on blood agar; presence or absence of granularity in fluid media. Clearance swabs were plated direct on to tellurite and examined in 48 hours. If growth had occurred sugar reactions were determined.

Ward Procedure.—Throat swabs were taken on admission and a preliminary laboratory diagnosis was obtainable by the following morning. This was confirmed later by subcultures and sugar reactions. Serum was given on clinical evidence, and where clinical and laboratory findings were at variance swabbing was repeated—often two or three times. Penicillin was being administered in the form of pastilles over a period of five days. It was not given until the diagnosis was certain, and it was considered desirable to wait five days after its last administration before starting the bacteriological investigation of the throat. As a result, clearance swabbing was not begun until the fifteenth to eighteenth day. Patients were swabbed—both nose and throat—on three consecutive days each week, until three negative swabs were obtained. Half of the cases clearing early had an additional swab or swabs beyond those necessary for clearance.

Material.—The period covered was from Jan. 1 to May 30, 1945, and records of 122 cases were available, 17 of which were not direct admissions. The latter are included, as they were observed for development of circulatory and neurological complications. In only one of these was the type of organism recorded, and they were excluded from investigations concerning duration of symptoms before admission, appearance of throat on admission, serum dosage, and, with the one exception, type of organism. Owing to the unexpected disbandment of the hospital a number of records were lost. Complete records of throat examinations were available only up to the end of April (Table I), but personal records of the actual cases of

TABLE I.—Throat swabs, January to April, 1945

Diphtheria	108
Vincent's angina .. .	39
Haemolytic streptococci .. .	985
Nil	33
Total	1,165

diphtheria were saved. The records of five cases were also lost, and these are incomplete as regards duration of symptoms, throat appearance, serum, and complications, but are available for type and, in all but one, throat clearance.

TABLE II

	Duration in Days							Total
	Less than 1	1-2	2-3	3-4	4-5	5-6	6-7	
No. of cases ..	38	29	11	8	1	2	1	90

The result has been some differences in the total number of cases in the various analyses, but the manner of their omission excludes the possible introduction of bias.

Types of Diphtheria.—Analysis of the first four months (Jan. to April, 1945) showed the following types: mitis 49, intermedius 9, gravis 34, morphological 16; total 108.

The figures shown (Table II) regarding the *duration of symptoms* before admission speak well for the effectiveness of the lecture demonstrations.

Clinical Diagnosis

It became obvious that membrane formation as a basis for clinical diagnosis was relatively useless. Many cases were seen too early for the formation of true membrane, and five presented with no exudate at all, but developed it the following day. All of these five were seen on their first day. True membrane was found in only 27 cases, the remainder having exudate—follicular to confluent in type—readily wiped off by the swab (Table III).

TABLE III

	Exudate			True Membrane	Total
	None	Follicular	Confluent		
No. of cases	5	19	39	27	90
Average duration of symptoms on admission (days)	1	1.9	2.0	2.5	

Marked oedema of uvula, palate, and tonsillar regions was observed in 41 cases, and faucial oedema came to be considered of importance diagnostically—it being relatively rarely observed in the ordinary streptococcal throat. A very characteristic presenting type was the “two-day quinsy”; the appearance was due to marked oedema in the region of the tonsil—membrane or exudate being hidden behind the swollen mass. This was regarded as practically diagnostic of toxic diphtheria.

To summarize, the diagnostic criteria were as follows: Cases with membrane and the “two-day quinsy” cases were considered as definite diphtheria. Those showing confluent exudate were treated as diphtheria until proved otherwise by repeatedly negative swabs. Follicular exudate was viewed with suspicion, and the presence of oedema of the fauces was taken as strongly suggestive even in the absence of exudate.

Hypertoxic Cases.—Seven cases showed marked toxæmia on admission. Four were of the “bullneck” variety, with oedema of the neck extending down over the clavicles, and one of these developed oedema of the glottis, requiring tracheotomy. All those observed long enough for its development—five—showed late neurological complications. None gave any evidence of serious cardiac involvement. The duration of symptoms before admission was 2-3 days in one case, 1-2 days in 4 cases, and less than 1 day in 2 cases.

Circulatory Complications.—No serious cardiac complications were seen, and what changes were observed were very difficult to assess. Two cases developed extrasystoles for a short period in their third week. Four cases showed a pulse rate persistently below 50 per minute, but as they were all highly trained Commandos it was thought that this was a convalescence bradycardia. Four cases had pulse rates over 100 per minute while at rest, but at least two of them were very nervous individuals and one had been in hospital previously with a “nervous heart.” Six cases showed tachycardia on leaving their beds for the first time. Seven cases had systolic blood pressures below 100—two on admission, the remainder at the end of the third week.

Neurological Complications

Out of a total of 101 cases observed long enough to develop neurological complications, 31 were reported as having done so. Five of these were doubtful, leaving 26 definite cases. The majority of these progressed no further than paralysis of the palate, which in many instances was very transient—lasting no longer than a week. Seven cases

had later involvement of the pharynx and limbs. Only two cases were recorded with accommodation paralysis, but, as it was never specifically inquired for, minor degrees were probably missed.

The average time of onset of paresis was: palate 26, accommodation 34, pharynx 42, limbs 48 days. No respiratory or trunk paresis was observed, but cases with widespread involvement of limbs were evacuated and may have developed it subsequently. Of 32 cases showing faucial oedema 46.9% developed neurological complications as compared with 19.6% in 46 without oedema, out of a total of 78 cases whose records were complete in both respects. This difference gives a χ^2 of 5.39 and $0.05 > P > 0.02$, and indicates the value of faucial oedema as a diagnostic sign.

Toxaemia seems to be the main factor influencing the development of neurological complications (Tables IV-VI) in that in this series they appear to be relatively unaffected by duration of symptoms prior to admission, by early clearance of the throat, and by the administration of serum.

TABLE IV

Clinical Signs of Severity	No. of Cases	Proportion Complicated
Nil	46	19.6%
Faucial oedema	27	37.1%
Bullneck	5	100%

TABLE V

Day of Disease when Admitted	No. of Cases	Proportion Complicated
1st	29	27.6%
2nd	27	33.3%
3rd	10	30.0%
4th and over	9	33.3%

TABLE VI

Throat Clear by 3rd Week	No. of Cases	Proportion Complicated
Yes	41	35.5%
No	26	26.9%

Serum at first sight appears, if anything, to promote the development of neurological complications, but the fact that the more toxic cases received more serum probably accounts for the discrepancy (Table VII).

TABLE VII

Serum in Units	No. of Cases	Proportion Showing Signs of Toxaemia	Proportion Complicated
0-48,000	24	33%	25%
49-80,000	36	39%	25%
81,000 +	18	56%	50%

As would be expected, gravis infections showed a higher percentage of cases with neurological involvement. A comparison of gravis with all other types gave $\chi^2=7.42$ and $P < 0.01$ (Table VIII).

TABLE VIII

Type	No. of Cases	Proportion Complicated
Gravis	27	48%
Intermedius	8	13%
Mitis	40	20%
Morphological	10	10%

Treatment and Management

Serum.—Serum was administered as soon as the clinical diagnosis was made, and was repeated next day if no improvement had occurred. An attempt was made to give the full dosage as a single injection, the degree of toxaemia being assessed on the first examination (Table IX). The

intravenous route was used only with a serum dosage of 100,000 units or over. Hypertoxic cases received 100,000 units intravenously and 60,000 to 100,000 units intramuscularly. In addition they received penicillin intramuscularly—20,000 units 3-hourly up to a total dosage of at least 1,000,000 units. They also received penicillin

TABLE IX.—Distribution of Serum Dosage

Dosage	No. of Cases
0-24,000	4
25,000-48,000	26
49,000-72,000	31
73,000-96,000	27
97,000-120,000	4
121,000-144,000	1
145,000-168,000	3
169,000-192,000	3
193,000-216,000	0
217,000-240,000	1
Total	100

pastilles by mouth. All patients were nursed flat for the first 21 days, or longer if complications intervened. Strict recumbency was not insisted on; they were allowed one pillow and were permitted to make themselves comfortable in bed.

Penicillin Pastilles.—Penicillin pastilles were prepared by the method of Martin (1944) with 500 units per pastille. They were available relatively late. The decision as to which case was to receive penicillin was decided by the toss of a coin—thus ensuring random selection. The only exceptions to this procedure were four of the hypertoxic cases. A total dosage of 200 pastilles over a period of five days was aimed at. The pastilles were held in the side of the mouth without sucking and continuously renewed. Twenty-four of the penicillin cases and 34 of the control series had been observed up to the 45th day, and the number still with positive throats at 5-day intervals was ascertained. Examination of Table X shows that the num-

TABLE X

Day:	1	15	20	25	30	35	40	45
Penicillin	24	8	4	3	2	1	1	1
Control	34	15	12	9	8	7	7	5

bers fell off in geometric proportion, as would be expected from general considerations and from the work of Hartley and Martin (1919-20). Hence, taking the logarithm of these figures, we got two series, the relation of which to time could be quite adequately represented by straight lines

(see Graph). Regression lines were calculated by the method of least squares, and gave the following formulae:

Letting y = number carrying on any particular day

Letting x = the particular day

Penicillin $\log_{10} y = 1.3529 - 0.03391 x$

Control $\log_{10} y = 1.4696 - 0.01765 x$

The first figure to the right of the equation is a function purely of the number of cases in each group. The second figure is an estimate, in the form of a regression coefficient, of the logarithm of the rate of clearance of each particular group—a figure which varies from epidemic to epidemic. The difference between these two regression coefficients—0.01627—is an index of the difference in rate of clearance between the two groups. This figure can be shown to be highly significant statistically, its standard error being 0.003338, giving a "t" of 4.88 and a probability for 12 degrees of freedom which is less than 0.001. The figures compare favourably with the formula obtained by Hartley and Martin:

$$\text{Log}_{10} y = 2.6002 - 0.0218 x$$

The statistical methods were derived from Fisher (1944), and Yates's correction for continuity was used throughout in the estimation of χ^2 .

Discussion

This epidemic has been described because it is felt that it is comparatively unusual in four points—namely, the short duration before admission, the large serum doses used, the age group covered, and the use of penicillin pastilles.

The short duration of symptoms before admission demonstrates the value of brief educational talks during epidemic periods. From the figures, prompt administration of an adequate dosage of serum does not appear to play any great part in preventing the development of palatal paresis, although it may limit the neurological involvement. On the other hand, it is felt that the low incidence and comparative triviality of the circulatory changes may be the result of the treatment. With regard to factors operating in the development of neurological complications this series is not ideal for studying the effects of duration of symptoms prior to admission, as the majority were seen on the first or second day. The fact that we are dealing with an adult population, presumably partially immune, is reflected in the difficulty of diagnosis of early cases. The comparatively late development of membrane in the partially immune has been pointed out by Neubauer (1943), who also noticed that exudate was readily wiped off without bleeding. That a number of cases later progressed to membrane formation indicates that the appearance of follicular and confluent exudate is a stage in the development of membrane. Pallor of mucous membrane was of little diagnostic use in this epidemic, as 40% had a concomitant streptococcal infection.

The series receiving penicillin was small, but the results are statistically quite definite, and it can be assumed that penicillin pastilles are effective in increasing the rate of clearance. A number of late carriers were also treated with penicillin pastilles. The impression was formed that it was much less effective in this type of case, but the numbers treated were too small to be certain of this.

Summary

An epidemic of diphtheria in adults has been described, notable for the short duration of symptoms before admission. Difficulties of diagnosis have been discussed and the results of a short series of cases treated with penicillin have been given.

We are indebted to the Director of Medical Services for permission to publish this paper. We wish to thank Brig. E. Bulmer, late R.A.M.C., and Lieut.-Col. W. Melville Arnott, R.A.M.C., for assistance, interest, and encouragement during the course of the investigation; and the nursing and medical staff—particularly Capt. Fitzpatrick, R.A.M.C.—for their thoroughness and care in dealing with the patients.

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PENICILLIN IN THE TREATMENT OF DIPHTHERIA

BY

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Diphtheria is one of the commonest causes of death among young children, and before the days of antitoxin serum it had a staggering mortality. Antitoxin has no doubt greatly reduced its mortality rate; nevertheless, it remains the most dangerous infectious disease to children. The sensitivity of *Corynebacterium diphtheriae* to penicillin is well known, but the therapeutic value of penicillin in diphtheria has not yet been ascertained.

Review of Literature

Christie and Preston (1946) reported two cases of malignant diphtheria with bull-neck treated with heavy doses of antitoxin serum and penicillin: one patient died and the other recovered. Richard J. Dodds (1946) reported 13 cases of diphtheria treated successfully with systemic penicillin in addition to normal doses of antitoxin. Ercoli, Lewis, and Moench (1945) reported experiments in which penicillin in a concentration of just over 1 unit per ml. inhibited *C. diphtheriae* *in vitro*. They induced experimental bacteraemia in mice by intraperitoneal injection of *C. diphtheriae* mixed with mucin. Subsequent injections of penicillin or sulphadiazine overcame the bacteraemia. However, when toxin was injected subcutaneously into rabbits or guinea-pigs it could not be counteracted by penicillin. A small inoculum of bacilli injected into guinea-pigs produced a local lesion with toxæmia just like human infection. In such cases they found that penicillin had negligible action. These observers concluded that penicillin might be of slight benefit in the prophylaxis of exposed contacts but that it could have no appreciable value in the treatment of patients suffering from clinical diphtheria, for which antitoxin should be given without any delay.

Penicillin in the treatment of diphtheria carriers appears to have been tried successfully by Berman and Spitz (1945). They treated 10 diphtheria carriers with penicillin solution containing 500 units per ml. four times daily: 1 ml. of this solution was instilled into each nostril and 1 ml. was sprayed into the throat with an atomizer. Within five days all reverted to a non-carrier state, whereas with a control group this took five to seven weeks. These observers believe that penicillin offers a quick and simple solution to the problem of diphtheria carriers. The fact that the organisms disappear quickly from the nasopharynx indicates that penicillin may be used as an adjunct in the treatment of clinical diphtheria. The replacement of antitoxin by penicillin, however, is not advocated.

It will be seen that there is no report of the use of penicillin without antitoxin serum in the treatment of clinical diphtheria. A trial of this nature is no doubt fraught with risk, as penicillin, although effective against *C. diphtheriae*, has no action on its toxin. The present study was undertaken with a view to ascertaining whether the drug can be used alone in place of the serum. The risk has been minimized by selecting early cases, under the assumption that