AN ANALYSIS OF 519 CASES OF DIPHTHERIA IN JOHANNESBURG 1951-1952

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It has recently been shown that diphtheria in South Africa is still a serious and widespread disease, responsible for 200-400 deaths annually.[1] It was therefore considered worth while surveying the clinical aspects of the disease, particularly with reference to the therapy.

The survey was carried out on 519 consecutive European patients admitted to a Johannesburg hospital during the 2 years 1951-52 and treated as diphtheria. A clinical analysis of the cases is presented in Table I.

TABLE I. CLINICAL FEATURES OF 519 EUROPEAN CASES OF DIPHTHERIA

	No. of Patients	%
Complications:		
Bullneck	93	18
Tracheotomy	27	5
Toxaemia	26	5
Myocarditis	94	18
Palatal Paralysis	36	7
Other Neurological Complications	30	6
Nephritis	26	5
Total with Complications	173	33·5
Recoveries:		
Complete	456	88
Discharged with Residual Defect	23	4
Deaths	40	7·7

Bullneck and myocarditis were the commonest complications in this series (each accounting for 18%), whilst the remainder each occurred in 5-7% of the cases. Tracheotomy is included as a complication although it is a form of therapy of a mechanical obstruction. The complication rate for the total material was 33·5%, which is rather low.[3, 17, 18] This might be due to early treatment, to a high proportion of immunized patients, or to a predominance of the *mitis* strain of *Corynebacterium diphtheriae*. There is hardly any reason to assume that patients are admitted to hospital earlier in Johannesburg than elsewhere. The proportion of immunized to non-immunized was the same as in England [2] and Copenhagen.[3] Murray [4] showed in 1942 that the *mitis* type was responsible for 85% of the cases in Johannesburg, and since no change has been found on later periodical surveys,[5] it can be assumed that the low complication rate is due to the *mitis* infection.

The cases that recovered completely amounted to 88%; 4% were discharged with residual defects, such as abnormal heart function (ECG), persistent palatal paralysis or peripheral neuritis, all of which are complications with a good prognosis if they occur late in the disease.[6, 3]

The case mortality was 7·7%, which is the highest reported in Johannesburg in the last decade.[1] This suggests, if the distribution of bacterial types has remained unchanged, that antibiotics, especially penicillin and sulpha drugs, which have been used extensively, are without influence in preventing death.

From these figures it is obvious that diphtheria in South Africa should not be considered as a disease of the past, but as a problem of current interest. On the other hand it is well known that a number of factors may influence or moderate the outcome of the disease. These will be analysed in this article and an attempt will be made to evaluate each one.

The age distribution of the 519 patients was similar to that found in a previous survey,[1] 50% being under 7 years and 75% under 12. The patients who had been actively immunized prior to admission were about 2 years older than the non-immunized, e.g. 50% of the immunized were under 7-8 years, whilst 50% of the non-immunized were under 6.

DIAGNOSIS

As early treatment of diphtheria is decisive in obtaining favourable results, it must once again be emphasized that the primary diagnosis in this disease is entirely clinical. If there are adequate clinical reasons for taking a swab for *C. diphtheriae* (KLB) the immediate use of

serum therapy is imperative. The only exception is the tracing of carriers.

Some information on the date of diagnosis can be extracted from Table II, where the cases are tabulated according to duration of obvious illness before admission

TABLE II. DURATION OF ILLNESS PRIOR TO ADMISSION

Duration of Illness before Admission (Days)	*No. of Patients*	*Cumulative No. of Patients*	*Cumulative Frequency %*
0—1.. ..	32	32	6·2
2	100	132	25·6
3	100	232	44·8
4	87	319	61·5
5	54	373	72·0
6	43	416	80·2
7	31	447	86·2
8—10 ..	36	483	93·0
>10.. ..	36	519	

to hospital. About 60% of the patients were admitted before the 5th day of illness, but 14% had been ill for a week before treatment.

In some cases a definitive diagnosis is extremely difficult, if not even impossible, in spite of careful clinical observation and extensive laboratory investigation. Clinical diphtheria cannot be excluded merely because KLB was not isolated. On the other hand, demonstration of KLB does not necessarily mean that the patient is suffering from the disease. He may be a carrier, or even a carrier with glandular fever, streptococcal tonsillitis or simple tonsillitis. Repeated antitoxin titration of the patient's blood might assist in some cases, but is seldom a practical procedure.

DEMONSTRATION OF C. DIPHTHERIAE

Table III illustrates the chances of demonstrating KLB at various times during the course of the disease provided the patient has not been treated with antibiotics. KLB

TABLE III. DEMONSTRATION OF *C. diphtheriae* IN RELATION TO DURATION OF ILLNESS BEFORE TREATMENT

Duration of Illness before Admission (Days)	*No. of Patients*	*Bacteriologically Positive*	*% Positive*
1	32	22	69
2	100	74	74
3	100	65	65
4	87	64	74
5	54	43	80
6	43	32	74
7	31	25	81
8—10 ..	36	28	78
>10.. ..	36	29	81

was found in nearly 75% of the patients (Copenhagen 1943-44: 85% bacteriological positive findings [3]). The stage of the disease does not affect the frequency with which KLB is isolated.

Although not statistically significant (perhaps because of the small numbers) the figures give the impression that KLB was isolated with increasing frequency up to the age of about 11 years, and less frequently thereafter

TABLE IV. DEMONSTRATION OF *C. diphtheriae* IN DIFFERENT AGE GROUPS

Age (Years)	*No. of Patients*	*Bacteriologically Positive*	*% Positive*
0—2.. ..	46	29	63
2—4.. ..	94	68	72
4—6.. ..	96	72	74
6—8.. ..	88	66	75
8—10 ..	53	48	90
10—12 ..	31	28	90
12—14 ..	29	19	65
14	82	52	63

(Table IV). In the young the smaller pharynx and a lack of cooperation might militate against obtaining a satisfactory specimen from the throat. It is more difficult to offer a satisfactory explanation for the older age groups.

The difference between the frequency with which KLB was isolated from the throat of immunized and non-immunized patients was not significant (Table V), an understandable finding because, as immunity against diphtheria is antitoxic and not antibacterial in nature, such an immunity will not prevent KLB from existing on the mucosa. If the host's immunity is poor or the

TABLE V. DEMONSTRATION OF *C. diphtheriae* RELATED TO PREVIOUS IMMUNIZATION

	No. of Patients	*Bacteriologically Positive*	*Bacteriologically Negative*	*% Positive*
Previously Immunized	168	128	40	76·2
Not Immunized ..	351	254	97	72·3
Total ..	519	382	137	73·7

resistance for other reasons diminished (secondary epidemiological factors, Anderson [34]) an attack of clinical diphtheria may occur, but if the host is well immunized KLB may live as a saprophyte for a period of time, thus rendering him a carrier. Immunity in diphtheria, as in many other diseases, prevents the effect but does not destroy the responsible agent itself.[7, 8] It will not be possible to discontinue prophylactic measures in the future.

It has already been mentioned that the demonstration of KLB does not conclusively clinch the diagnosis of diphtheria. The question arises whether the 137 patients who were bacteriologically negative (Table V) had clinical diphtheria. In Table VI the cases are divided according to the demonstration of *C. diphtheriae*, and

TABLE VI. BACTERIOLOGICAL FINDINGS IN IMMUNIZED AND NON-IMMUNIZED CASES OF CLINICAL DIPHTHERIA

			No. of Patients	*No. with Complications*	*%*	*No. of Deaths*	*%*
CD +	382	I	128	31	24·2	3	2·3
		NI	254	98	38·6	21	8·3
CD —	137	I	40	10	25·0	2	5·0
		NI	97	34	35·1	14	14·5

CD + = *C. diphtheriae* was isolated
CD — = *C. diphtheriae* was not isolated
I = Immunized
NI = Not immunized

Comparing the complication rates in:
(i) CD+, (I) and CD—, (I): t=0·10 P=0·9
(ii) CD+, (NI) and CD—, (NI): t=0·61 P=0·3

each group subdivided into non-immunized and immunized. As a standard immunization one accepted 2 injections of toxoid at an interval of 4-8 weeks, provided the last injection was not later than 1 month before the illness.

If there were about the same degree of clinical diphtheria in the bacteriological negative group as in the bacteriological positive group we could expect to find the same complication rate in comparable subgroups. Statistical analysis shows that there is no significant difference in the complication rates of the immunized groups (Table VI; CD+, (I) and CD−, (I); P=0·9) or of the non-immunized groups (CD+, NI and CD−, NI; P=0·3) whether KLB was isolated or not. It may therefore be concluded that diagnosis on clinical grounds was accurate and that the isolation of KLB although of great value is not a *sine qua non* in establishing diagnosis.

All the positive bacteriological reports were based on cultural and morphological observations. Of the cultures reported positive, 96 were tested for toxigenicity by guinea-pig inoculation. The results are tabulated in Table VII.

A statistical analysis revealed that there was no significant difference in complication rates between the groups in which KLB was toxigenic and that in which the bacteriological diagnosis was established on morphological and cultural findings only, nor was there any difference in the incidence of complication rates between the non-immunized of the toxigenic group and the

TABLE VII. THE TOXIGENICITY OF *C. diphtheriae* RELATED TO THE CLINICAL COURSE (382 CASES)

			No. of Patients	*No. with Complications*	%
CD + Toxigenic	83	I	27	8	30
		NI	56	22	39
CD + Non-Toxigenic	13	I	6	1	17
		NI	7	2	29
CD + Not Tested	286	I	95	22	23
		NI	191	74	39

Abbreviations: See Table VI

Comparing the complication rates in:

(i) CD + (Tox., I) and CD + (Not tested, I): t = 0·66, P = 0·3

(ii) CD + (Tox., NI) and CD — (NI) (see Table VI): t = 0·53 P = 0·3

group with negative bacteriological findings (P=0·3). KLB was found non-toxigenic in 13 (14%) of the cases tested. Although these figures are too small for statistical analysis, it may be noted that complications also occurred in this group. The conclusion is that a correct clinical diagnosis was not dependent on the isolation of toxigenic *C. diphtheriae*.

THE SIGNIFICANCE OF DURATION OF ILLNESS PRIOR TO ADMISSION TO THE FINAL OUTCOME

Table II shows the duration of illness before hospitalization. From data available in this study it is apparent that the distribution of the patients, whether immunized or not, in the various age groups (2-year periods) is homogeneous and therefore need not be further considered.

The duration of illness before admission, which in 90% of the cases is synonymous with the initiation of treatment, is in Table VIII correlated with complication rates and death rates. These rates vary from day to day but if the figures are smoothed by using a moving average of 3 groups we get a clearer picture. The results are expressed graphically in Fig. 1.

The moving averages indicate the importance of an

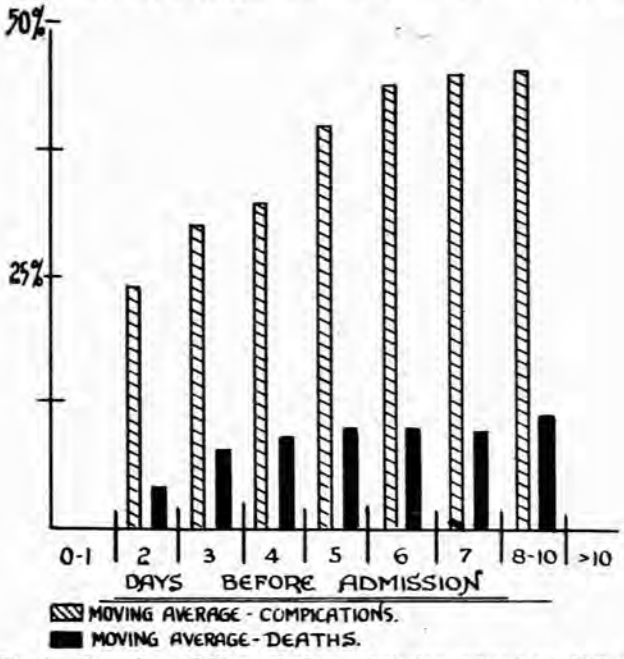

Fig. 1. Duration of illness before admission related to clinical course of diphtheria.

TABLE VIII. DURATION OF ILLNESS BEFORE ADMISSION RELATED TO CLINICAL COURSE OF DIPHTHERIA

Duration of Illness before Admission (Days)	*No. of Patients*	*No. with Complications*	%	*Moving Average of 3 Groups* %	*No. of Deaths*	%	*Moving Average of 3 Groups* %
0—1	32	4	13		—	—	
2	100	28	28	24·1	4	4	4·3
3	100	24	24	29·3	6	6	7·0
4	87	32	37	31·5	10	11	8·7
5	54	20	37	39·1	5	9	10·3
6	43	20	47	43·0	4	9	10·2
7	31	15	48	43·6	4	13	10·0
8—10	36	13	36	43·7	3	8	10·7
>10	36	17	47		4	11	

TABLE IX. SITUATION OF DIPHTHERITIC FOCI RELATED TO CLINICAL COURSE

	Single Focus				*Two or More Foci*							
	Tonsil Membr. Ex.	*Tonsil Follic. Ex.*	*Nasal*	*Laryngeal*	*Tonsil Membr. Ex. + Nasal*	*Tonsil Membr. Ex. + Laryng.*	*Tonsil Membr. Ex. + Nasal + Laryng.*	*Tonsil Follic. Ex. + Nasal*	*Tonsil Follic. Ex. + Laryng.*	*Nasal + Laryng.*	*No Tonsillar Ex. or Nasal or Laryng. Symptoms*	*Total*
No. of Patients	258	111	16	4	41	36	4	5	5	1	38	519
Complications:												
Bullneck	66	—	1	1	14	7	2	—	—	—	2	93
Tracheotomy	—	—	—	1	—	20	3	—	2	1	—	27
Toxaemia	11	—	—	—	6	7	2	—	—	—	—	26
Myocarditis	47	12	1	1	12	15	2	—	—	—	4	94
Palatal Paralysis ..	24	—	—	—	4	2	—	—	—	—	6	36
Other Neurological Complications	17	—	1	1	4	3	—	—	—	—	4	30
Nephritis	15	2	—	—	3	3	1	—	1	—	1	26
No. with Complications	91	14	1	1	22	30	4	—	2	1	7	173
%	35	13	6	25	54	83	100	—	40	—	19	33·5
Complete Recoveries ..	229	107	16	3	32	24	1	5	4	—	35	456
Discharged with Residual Defect	15	2	—	1	2	1	—	—	—	—	2	23
No. of Deaths	14	2	—	—	7	11	3	—	1	1	1	40
%	5·4	1·8	—	—	17	30	75	—	20	—	3	7·7

Ex. = exudate, membr. = membranous, follic. = follicular, laryng. = laryngeal.

early diagnosis because the chance of complications arising and death ensuing increase *pari passu* with delay in treatment, subject to the reservation that treatment plays little or no part if the delay has extended to 5 days or more. This observation is supported by Amies' experiments in guinea-pigs.[9] He found that the time of the injection of antitoxin into intoxicated or infected animals was of much greater importance than the amount injected. Paschlau's observations[10] in Berlin support this contention. He found that the death rate among 197 diphtheria patients who were treated within the first 48 hours of correct diagnosis was 1·96%, whereas it was 8·9% among general diphtheria patients in Berlin.

The effect of antitoxin therapy on patients with diphtheria has been a subject for controversy ever since Behring's time. Although clinicians do not doubt the favourable influence of antitoxin, really convincing positive evidence has proved difficult to come by. Amies' and Paschlau's observations on the absolute necessity for early antitoxin treatment is further supported by this survey, which suggests that its beneficial effect in man is limited to the first 4-5 days of illness and that at present nothing can be expected from specific treatment at any later date.

THE DIPHTHERIA FOCUS OR FOCI

A summary of the clinical course related to the localization of the diphtheria focus or foci is presented in Table IX (a differentiation between tonsillar and pharyngeal cases as recommended by Top[11] was not feasible in this series). The tonsils were affected in 90% and they constituted the only focus in 71% of the cases. The membranous form was by far the most frequent (2/3rds of all cases).

Comparison of *complication rates* in selected groups:

(i) Tonsil membr. ex.—Tonsil follic. ex.
$x^2 = 18 \cdot 43$ $P << 0 \cdot 01$

(ii) Tonsil membr. ex.—Tonsil membr. ex. + nasal
$x^2 = 5 \cdot 60$ $P = 0 \cdot 02$

(iii) Tonsil membr. ex.—Tonsil membr. ex. + laryng.
$x^2 = 29 \cdot 33$ $P << 0 \cdot 01$

(iv) Tonsil membr. ex. + nasal—Tonsil membr. ex. + laryng.
$x^2 = 8 \cdot 45$ $P < 0 \cdot 01$

Comparison of *death rates* in the same groups:

(i) $x^2 = 2 \cdot 74$ $P = 0 \cdot 01$
(ii) $x^2 = 6 \cdot 71$ $P = 0 \cdot 01$
(iii) $x^2 = 26 \cdot 44$ $P << 0 \cdot 01$
(iv) $x^2 = 2 \cdot 63$ $P = 0 \cdot 1$

Single focus. The diphtheritic foci met in this study were of 3 types: (*a*) Tonsillar, where the exudate was either of the membranous type or the follicular type, (*b*) nasal, and (*c*) laryngeal. There was one case of diphtheria of the skin as a complication to a tonsillar-membranous type. Table IX shows that toxaemia and palatal paralysis were restricted to the tonsillar-membranous form, which also included most of the cases of myocarditis, 'other neurological complications' and nephritis.

On statistical examination of the tonsillar-membranous type, against the tonsillar-follicular type there was found a significantly higher complication rate ($P << 0 \cdot 01$) in the former as compared with the latter group, whereas there was no significant difference in death rates. No importance can be attached to the death-rate comparison

as there were only 2 deaths in the tonsillar-follicular type.

The 2 other groups are too small for statistical calculation. However, they cannot be neglected; in them complications such as myocarditis, tracheotomy and peripheral neuritis occurred. It can be concluded that the type of tonsillar exudate has a bearing on the prognosis, being more serious when membranes are present. Laryngeal diphtheria is serious, whereas nasal diphtheria has a good prognosis. Similar observations were made by Hartley *et al.*[2]

Two or more foci. Again the majority of complications are found in the tonsillar-membranous type. For example all toxaemia, myocarditis and neurological complications occurred in this group. But the presence of a second focus increases the complication rate and death rate considerably. There is a statistically significant difference between complication rate and death rate of the isolated tonsillar-membranous type on the one hand and the same form combined with either nasal or laryngeal diphtheria. The prognosis for the tonsillar-follicular form is good if the second focus is in the nose, but more serious if it is in the larynx. The combination of nasal and laryngeal diphtheria seems to be a rarity. The larynx was affected in 10% of the patients, in half of whom tracheotomy was carried out. Chigier [12] found a tracheotomy rate of 3% in non-European cases from South Africa; the rate was 1% on Tyneside 1941-43 [2] and nil at Coseley 1951.[13]

Finally there were 38 patients without exudates on the tonsils and without nasal or laryngeal symptoms. Nevertheless it is evident from Table IX that these were cases of clinical diphtheria. The complication rate in this group was greater than in those with tonsillar-follicular exudate as a single focus. It is interesting to observe that in 7 patients a relatively small number of early complications and a comparatively large number of late complications (myocarditis, neurological complications) occurred. This suggests *a priori* that these patients had been neglected in the acute phase. This was confirmed in that none of them was admitted to hospital before the 6th day of illness; 3 were admitted after the 15 thday, 1 of whom died, and her history is as follows:

Female, 4 years old. Not immunized; several attacks of sore throat during 5-6 weeks immediately preceding admission; developed weakness in the legs 10 days, nasal speech 7 days, and difficulty in swallowing 4 days before admission. No specific treatment had been given. Died from myocarditis a week after admission.

A diagnosis of diphtheria was made in 31 patients who presented no localized symptoms or complications. *C. diphtheriae* was isolated from 27 of them and this was obviously the reason for the diagnosis and treatment. It remains doubtful, however, whether they were in fact suffering from diphtheria or whether they were diphtheria carriers with some other disease which, in most cases, was a sore throat. It should be mentioned that the 31 uncomplicated cases showed the same distribution with regard to day of admission, as illustrated in the rest of material (Table II).

To sum up: Tonsillitis complicated with membranous exudate was the most frequent lesion and in people so affected toxic complications were most frequently encountered. Laryngeal diphtheria, although rarely occurring alone, always gave cause for anxiety because of the associated respiratory obstruction, whereas nasal diphtheria or tonsillitis with follicular exudate allowed of a much more favourable prognosis.

COMPLICATION AND DEATHS RELATED TO AGE

It is of interest to analyse the material with reference to age because in South Africa the primary immunization course is commonly given late,[14] presumably at school. Table X illustrates the percentage of complications

TABLE X. COMPLICATIONS AND DEATHS WHICH OCCURRED BEFORE SCHOOL-GOING AGE (IMMUNIZED AND NON-IMMUNIZED)

	Total Cases	*Cases under 6-Years Old*	%
Bullneck	93	48	52
Tracheotomy	27	25	93
Toxaemia	26	18	69
Myocarditis	94	53	56
Palatal Paralysis	36	18	50
Other Neurological Complications	30	17	57
Nephritis	26	15	58
Deaths	40	30	75

and deaths which occurred before 6 years of age. Most of the complications, practically all the tracheotomies, and 75% of the deaths occurred below the age of 6 years. Because of this the primary course of immunization should be given at an age much earlier than 6 years

TABLE XI. COMPLICATIONS AND DEATHS RELATED TO AGE

	Patients under 6 Years	*Patients over 6 Years*
Myocarditis only	33 (8)	35 (5)
Myocarditis + Toxaemia ..	11 (10)	5 (3)
Myocarditis + Tracheotomy	7 (1)	1 (0)
Myocarditis + Tox. + Trach.	2 (2)	—
Toxaemia	1 (1)	3 (1)
Tracheotomy	12 (5)	1 (1)
Toxaemia + Tracheotomy ..	4 (3)	—
Total	70 (30=43%)	45 (10=22%)

Figures in brackets = number of deaths in the group

(cf. Woodrow, Cape Town, 1946 [15]). All deaths occurred in association with myocarditis, toxaemia or tracheotomy. The total number of each of these complications, their combinations and the number of fatal cases in each group is tabulated in Table XI in regard to age.

It will be observed that, while the prognosis for each of the complications is more serious in the younger age-groups, toxaemia is the most dangerous and that tracheotomy cases, as observed by Chigier [12] and Bayer,[16] carry a 50% mortality. Myocarditis occurred rather frequently in the older age-groups.[3] The total figures show that there is, for the same group of complications, a mortality of 43% in patients below 6 years old as against 22% in those above this age. However, conclusions should not be drawn from these last figures without some knowledge of the state of active immunity of the patients in the age-groups.

ACTIVELY IMMUNIZED AND NON-IMMUNIZED

The effect of immunization is shown by the data in Table XII.

TABLE XII. COMPLICATIONS AND DEATHS IN IMMUNIZED AND NON-IMMUNIZED PATIENTS

TOTAL OF ALL CASES

	No. of Patients	*No. with Complications*	%	*No. of Deaths*	%
Immunized	168	41	24·4	5	3·0
Non-Immunized ..	351	132	37·6	35	10·0

Comparing

(i) Complications of I and NI: $t = 3 \cdot 14$, $P = 0 \cdot 001$

(ii) Death rates of I and NI: $x^2 = 7 \cdot 72$, $P < 0 \cdot 01$

There was a history of immunization in 32·5% of the patients, which is higher than the figures from Cape Town [15] but similar to those from Gateshead 1944 [2] and Copenhagen 1943-44.[3] It does not mean that the immunization of the individual has been unsuccessful, but that the percentage of the population actively immunized was insufficient. Without knowing this percentage we can form no opinion of the effect of prophylactic endeavours on the morbidity. The effect on individual cases, however, is significant for both complication rate ($P=0 \cdot 001$) and death rate ($P<0 \cdot 01$), which accords with the observations of others [3, 7, 17, 18] that the prophylactic injections moderate the clinical course of diphtheria. As it is most unusual for diphtheria to terminate fatally in immunized patients [2, 3] the 5 cases found in this series will be shortly described.

Case 1. Female, 4 years old. Immunized when 6 months old (2 injections of combined whooping cough and diphtheria prophylactic). Ill with sore throat 3 days before admission, vomiting and convulsions the day before. On admission moderately ill with extensive white membranes obscuring both tonsils. Moderate bullneck. In spite of therapy developed a palatal paralysis and pheripheral neuritis and about a week later myocarditis with fatal termination. *C. diphtheriae* was isolated before admission.

Case 2. Male, 3 years old. Immunized with 2 injections a few months before illness. Had been ill with sore throat for 5 days. Diagnosed as follicular tonsillitis. Became suddenly worse the day of admission and received artificial respiration on the way to hospital. On admission, moribund with signs of laryngeal obstruction. Died 5 minutes later. Pharynx was filled with membranous material. *C. diphtheriae* was isolated after death.

Case 3. Male, 5 years old. Immunized when 4 years old (number of injections not stated). Two weeks before admission, an attack of croup, treated as a non-specific laryngitis. Four days before admission developed a sore throat increasing in severity, followed by respiratory difficulty 3 days later. The patient was extremely ill on admission and had cervical adenopathy; there was no membrane in the throat, but severe laryngeal obstruction. Tracheotomy was performed immediately, but the patient died 24 hours later with symptoms of heart failure.

Case 4. Male, 5 years old. Immunized when 2 years old (number of injections not stated). Four days before admission, sore throat, pyrexia and headache. The day before admission, hoarseness, slight convulsions and respiratory difficulty. On admission, toxic, mild respiratory distress, enlarged cervical glands with slight periglandular oedema, and enlarged tonsils covered with membranes. The condition improved for the first few days. A week later, myocardial affection and peripheral vascular failure with fatal termination in a few hours. Toxigenic *C. diphtheriae* was isolated from the throat.

Case 5. Female, 11 months old. Immunized 2 months before illness (number of injections not stated). Four days before admission, a slight cold. Respiratory difficulty 12 hours before admission. First medical attention a few hours before hospitalization. Patient seriously ill, cyanotic, pronounced croup. Membranes on tonsils. Tracheotomy performed immediately with good results, but the toxaemia progressed and the patient died 3 days later with signs of pulmonary affection. *C. diphtheriae was not isolated.*

There can be no doubt that the first 2 patients had received a full primary course of diphtheria immunization, and yet they developed malignant diphtheria. An earlier diagnosis should have been possible in both cases, especially in case 1, and might have resulted in a favourable outcome. It is not known if the last 3 patients had been fully immunized but, even so, cases 3 and 4 could have been diagnosed at an earlier date. As previously stated diagnosis can be very difficult, but it is clear from these examples that diphtheria should always be borne in mind even when patients are known to have been immunized. Further, a small number of patients are relatively refractory to immunization and thus may contract a malignant diphtheria equivalent to that in a non-immunized person. Finally, diphtheria prophylactic is not always stored under optimal conditions.

In spite of the 5 deaths, of whom 2 certainly were immunized and 3 probably, it must be concluded that individual immunization is generally successful.

Treatment

Antitoxin and penicillin were used as standard treatment. The results in Table VIII and the diagram can probably be attributed to the effect of antitoxin treatment, whereas penicillin seems to be without influence on the actual disease. Other antibiotics such as streptomycin, aureomycin, terramycin, and the sulphonamide drugs were given to a small number of patients, too small to allow of conclusions. Cortisone or ACTH was given to those who were very ill, but the true effect cannot be gauged, partly because of the case selection employed and partly because of the small number. Similarly, the general effect of glucose and oxygen cannot be appraised because they were given only to selected patients.

Financial Aspects

From previously published figures from Johannesburg[1] it was found that 164 Europeans with diphtheria spent 5,137 days in hospital, giving an average of 31 days per patient. This compares with 53 days per patient in England.[13] The cost per patient per day was 55s., and as the number of patients per year in this series was 260 (the 519 were the total of 2 years) the expenses for a period of 1 year were £22,165.

Similar calculations for non-Europeans in Johannesburg [1] showed that 398 patients were 8,858 days in hospital with an average of 22 days and at a cost of 20·5s. per day. If the notification rate is estimated at 70 per 100,000,[1] there is an annual total of 325 cases, and as all cases are hospitalized there must be an expenditure of £7,340 per year.

Consequently, the city of Johannesburg is paying approximately £30,000 annually for treatment of hospitalized diphtheria patients and at the same time maintaining an immunization clinic, which so far has been without influence on the morbidity of the disease.

It can only be regretted that the public does not make better use of the facilities offered to them.

DISCUSSION

In general the diagnosis appeared to be correct; in only 30 cases was there doubt. Accepting the figures, the question arises as to how the complications and death rate may be further reduced.

Administration of antitoxin before the 5th day of illness has been shown to be of primary importance in this series where *C. diphtheriae* type *mitis* was responsible for 85% of the cases.[4, 5] As the difference in 'virulence' of the 3 diphtheria types can be explained as their ability to produce toxin rapidly (*gravis*) or slowly (*mitis*),[19, 20] it would be expected that the maximum 5-day limit for antitoxin administration would be considerably shorter in gravis and intermedius infections. This corresponds with Paschlau's finding [10] in a series of cases of 'malignant diphtheria', that if antitoxin was given after the 2nd day of illness it was without effect on the disease. It also accords with Amies' observation [9] that the time of antitoxin treatment was more important than the dose of antitoxin. This would explain the severe course of *gravis* infection [2, 21] without postulating sero-resistant cases [21, 2] or the presence of two or more types of toxin.[22] Consequently the first aim must be that of early diagnosis. This, in fact, is about all that can be done at present in clinical diphtheria.

Antibiotics. Penicillin inhibits the multiplication of *C. diphtheriae*,[23, 24] but it is almost certain that it has no influence on the absorption of toxin or on its pathological action.[25, 26, 27] However, Hewitt [28] has shown that guinea-pigs experimentally infected with a suspension of toxigenic diphtheria organisms and treated with terramycin die 1-6 days later than either control animals or penicillin-treated animals.[23] Administration of a small amount of antitoxin, sufficient to neutralize the toxin injected with the suspension, did not prevent death. It was therefore concluded that the toxin was produced during the terramycin treatment, and that the terramycin had no influence on its action though it did delay death.

Lall and Karelitz [29] treated 6 cases of diphtheria with antitoxin and terramycin and 6 diphtheria carriers with terramycin only. None of the patients developed any complications, and they were all bacteriologically negative in less than a week (an average of 2⅓ days). The reports are interesting, but only observations on a large scale will show whether these favourable results with terramycin are of true value in the treatment of diphtheria.

Glucose. Amies [30] found that toxin formation *in vitro* was inhibited by a glucose concentration of $\pm 0 \cdot 25\%$ and that a dissociation of toxigenic to atoxigenic organisms occurred at a glucose level of $\pm 0 \cdot 075\%$. Harries and Mitman [31] advocate the use of glucose intravenously in cases of toxaemia and myocarditis, partly because it should serve as an energy supply for vital organs, partly because glucose is believed to protect the heart muscle from the effect of the toxin. Friis-Hansen *et al.*[32] found experimentally a reduced glucose-tolerance in rabbits exposed to various amounts of diphtheria toxin. Formal proof of the value of glucose administration in diphtheria-therapy is still lacking.

Cortisone and related compounds. Very little has been written on the use of cortisone in the treatment of diphtheria. Rosenbaum and Obrinksy's work [33] dealing with its effect in experimentally infected guinea-pigs is one of the few publications on the subject. Cortisone could not apparently prevent death or significantly increase the survival time, nor could it prevent adrenal haemorrhages. On the other hand, it did not interfere with the protective action of antitoxin. The experiments do not suggest that cortisone is of real value in the treatment of diphtheria. However, our knowledge of cortisone and related products is still very inadequate and extensive studies are needed before their values can be assessed.

In brief: the only effective therapeutic agent we possess is antitoxin but its value is limited to the early stages of the disease. Because it will be given too late in a number of cases, the best method of preventing death from diphtheria is active immunization.

SUMMARY

1. A description of 519 relatively mild cases of diphtheria is given.

2. *C. diphtheriae* was demonstrated in 73·7% of the cases. The chance of isolating *C. diphtheriae* was the same early and late in the disease and was independent of previous active immunization. There was evidence that it was more difficult to demonstrate the organisms in the members of the youngest age-groups.

3. Complications were not more frequent in patients in whom *C. diphtheriae* was isolated than in those in whom it was not.

4. The diphtheric focus and the combination of diphtheric foci were of prognostic value. Nearly all toxic complications occurred in connexion with membranous exudate on the tonsils.

5. 75% of the deaths and the majority of complications occurred in children below the age of 6 years.

6. Antitoxin was found to be the only remedy of value in the treatment of the disease, but its effect is limited to the first 4 days of illness when type *mitis* is the responsible agent. In *gravis* infections, however, it appears from the literature that the time limit for beneficial effect of antitoxin treatment is restricted to the first 2 days of illness.

7. Only 60% of the cases were admitted before the 5th day of illness.

8. The expenditure in Johannesburg on the hospitalization of diphtheria patients is assessed at approximately £30,000 a year.

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