those concerned directly with reproduction. The elucidation of the physiological part played by these and other metals found constantly in minute traces in the body offers a promising field of work.

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DIPHTHERIA IN THE DUNEDIN HOSPITAL, 1921-31

A Statistical and Clinical Study

BY

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In recent years there has been a disconcerting recrudescence of diphtheria in many parts of the world. Twenty-two out of twenty-eight European countries record this experience. Coincidentally with increased morbidity several countries, notably Germany and Russia, have experienced a great increase in case mortality. This seems to be due to a more toxic form of disease, which is proving intractable to the usual doses of antitoxin, and which is attended by severe cardiac and nervous complications.

In New Zealand since 1912, and particularly since 1921, diphtheria incidence has steadily declined. Thus in 1921 notifications were 2,611 (21 per 10,000 of mean population) and deaths 107 (0.87 per 10,000), whereas in 1930 notifications were 1,440 (10 per 10,000) and deaths 58 (0.41 per 10,000). There was no evidence of undue toxicity until 1929, when a few cases of the new type occurred in the Dunedin Hospital. The occurrence of more cases of the kind in 1930–1 has given occasion for this report, and to illustrate it we have to review the incidence of diphtheria in the Otago Hospital District and in the Dunedin Hospital.

Morbidity Data

For the period 1921–31 inclusive the total number of cases notified in Otago was 1,319, the population in 1921 being 137,062 and the estimated population in 1931 152,600. Of these cases 847 (64.2 per cent.) were admitted to the Dunedin Hospital. (In Otago, and in New Zealand generally, practically 100 per cent. of notified cases are admitted to hospital.) The annual numbers and rates are shown below.

Table I.—*Number of cases of diphtheria notified in the Otago Health District during the period 1921–31, rate per 10,000 of population, and number admitted to the Dunedin Hospital.*

Year	Cases of Diphtheria Notified in Otago	Rate per 10,000 of Mean Population	Cases of Diphtheria Admitted to Dunedin Hospital	Percentage of Total Admissions
1921	356	25.60	225	8.33
1922	149	11.02	135	5.08
1923	70	5.05	55	2.04
1924	190	13.40	168	5.55
1925	147	10.50	84	2.03
1926	211	14.90	68	1.67
1927	29	2.05	15	0.38
1928	15	1.02	4	0.09
1929	12	0.81	4	0.09
1930	43	2.90	32	0.75
1931	97	6.50	57	1.33
Total ...	1,319	—	847	2.11

This table shows that the greatest incidence was in the years 1921, 1922, and 1924, and that a notable fall occurred in the years 1927, 1928, and 1929. During the period 1921–4 Schick testing and active immunization was carried out in Otago, and some 1,250 children were immunized. The work was done by students in the Preventive Medicine Class at the University of Otago, with the consent and close co-operation of the Health Department. We venture to assume that the 1927–9 decline in incidence was in part due to this work, and support is lent to this assumption by experience at a school known as the North-East Valley School. This school was fully immunized in 1927; a small outbreak occurred there in 1930, but the disease was confined to children who were below the school age in 1927. The unfortunate Bundaberg disaster of January, 1928, in which twelve out of twenty-one children inoculated for diphtheria died, led to the temporary suspension of diphtheria immunization in Otago.

Age Incidence

Table II shows that the largest number of cases in our series occurs in the 5–15 age period, but that 34 per cent. of the total cases occurred in the age group 15 and over.

Table II.—*Age distribution of diphtheria cases in the Dunedin Hospital and deaths for the five years 1927–31.*

Age Period in Years	Total Cases	Total Deaths	Age Period in Years	Total Cases	Total Deaths	Age Period in Years	Total Cases	Total Deaths
0-1	1	0	5-6	5	0	15-20	14	0
1-2	0	0	6-7	6	1	20-25	10	0
2-3	5	2	7-8	5	0	Over 25	14	0
3 4	8	2	8-9	7	0			
4-5	6	3	9-10	9	0			
			10-15	21	2	Total ...	38	0
Total ...	20	7	Total ...	53	3	All ages	111	10

It is usually stated that diphtheria occurs chiefly in children under 15 years of age, and that the maximum frequency is reached between the second and fifth year. In a recent study by Goodall, Greenwood, and Russell

(1931), over 91 per cent. of a series of 110,745 cases occurring in the London Metropolitan Asylums Board hospitals were in children under 15 years.

Case Mortality

There has been a disquieting increase in case mortality during the last three years as shown in Table III, where the figures for the two periods 1921–8 and 1929–31 are contrasted.

Table III.—*Case mortality for diphtheria in the Dunedin Hospital for 1921–8 and 1929–31.*

Period	Number of Cases	Number of Deaths	Case Mortality
1921–28	754	12	1.59
1929–31	93	11	11.82

The interval between onset of disease and time of administration of serum is much the same in both series; but in 1929–31 the dose of antitoxin was much larger. Until 1930 the usual dose was from 4,000 to 10,000 units, but during 1930–1 we found that with some patients doses even four and five times as large were ineffective. At first we doubted the potency of our serum, but two brands tested on guinea-pigs gave full protection from bacilli obtained from our worst cases.

Observations in other countries show that where morbidity rates are low case mortality rates are high. Bulgaria, with a morbidity rate of 2.9 per 10,000, has a case mortality of 14.6. Rumania, with a morbidity of 1.8 per 10,000, has a case mortality of 16.2. Present knowledge gives no indication of the cause of this case mortality. As a working hypothesis we assume a fluctuation in the virulence or toxigenicity of the bacillus; but the important changes which occur in the herd immunity of the district cannot be ignored, nor can they be assessed accurately. Table II shows that the fatality rate is highest in the age period 0–5 years when 70 per cent. of the deaths occur.

Seasonal Fluctuations

Table IV shows the seasonal fluctuations in cases admitted to the Dunedin Hospital during 1921–31.

Table IV.—*Seasonal incidence of diphtheria in Dunedin Hospital 1921–31.*

	Summer		Autumn		Winter		Spring		Total
	A	B	A	B	A	B	A	B	
1921	125	51	39	17	19	8	42	19	225
1922	53	39	28	21	25	19	29	21	135
1923	15	27	14	25	17	31	9	16	55
1924	72	43	4	2	62	37	30	18	168
1925	20	24	17	20	24	29	23	27	84
1926	34	50	10	15	9	13	15	22	68
1927	6	40	3	20	3	20	3	20	15
1928	2	50	0	0	1	25	1	25	4
1929	1	25	2	50	1	25	0	0	4
1930	2	6	16	50	13	41	1	3	32
1931	7	12	34	60	16	28	0	0	57
Total	337	40	167	20	190	22	153	18	847

A=Number of cases; B=number of cases expressed as a percentage of the annual diphtheria admissions.

Seasonal fluctuations are remarkably constant in Europe, America, Africa, and Japan, mid-summer being the period of lowest prevalence. Incidence increases with the advent of cold weather, and reaches its maximum in mid-winter. Australia, on the other hand, shows a summer peak and a winter drop. As in Australia, summer incidence in New Zealand is definitely the highest, but the winter drop is much less pronounced. Dunedin is in the zone of the prevailing westerlies, and autumn is distinctly warmer than spring. This departure from the seasonal fluctuations in northern latitudes may be due to climatic conditions, but the point requires further investigation.

Form of Disease: Antitoxin Dosage

Clinically the small epidemics of 1930–1 have been remarkable for the general severity of the disease and for the large doses of antitoxin required. Thus eighteen patients coming under treatment on the second day of the disease received an initial dose of 24,000 units; eleven first treated on the third day received 64,000 units.

One of us (H. W.) has had experience (1925–6) of epidemic diphtheria in the practice of two hospitals in Sydney. He is convinced that some of our cases were exceptionally malignant. While most of them were of the familiar type, with limited membrane, slight toxaemia, little inflammatory reaction or glandular enlargement, and rare complications and ready response to antitoxin, in this particular type the membrane was widespread, invading the palate or pharynx, the toxaemia was severe, inflammatory reaction was pronounced, glandular enlargement and swelling of the neck were great, the breath was fetid, myocarditis, albuminuria, and paralysis were frequent, and there was no response at all to antitoxin in ordinary doses. These two separate clinical types of the disease were distinguished by Anderson and his collaborators (1931), and our 1930–1 cases conform to their description. These authors further claim to have correlated the clinical types with separate forms of the bacillus recognizable in the laboratory. We have noticed that the severe cases in this series have been associated with a shorter, less granular type of bacillus, but we have not sufficient data to permit the recognition of *B. diphtheriae gravis*. The description of the special medium for differentiating the strains reached New Zealand too late for its adoption in this series. All the strains were tested for virulence on guinea-pigs, by the intracutaneous method, with positive results.

Finding that patients affected by the grave "bull-neck" type of the disease did not improve after intramuscular injections of 40,000–60,000 units, we supplemented the intramuscular dose by larger doses given intravenously. In each case we endeavoured to estimate the amount required to cure. This we give all at once, avoiding repeated dosage. Occasionally we gave as much as 200,000 units as an initial dose, 50,000–80,000 units intramuscularly and 120,000–150,000 units intravenously. If this was ineffective within twenty-four to thirty-six hours more serum was given. We believe that the injection of these large doses, twice or even thrice repeated, succeeded where less vigorous treatment would have failed. Intravenous injection is dangerous unless given slowly and skilfully, for the patient is often a small child and may be suffering from severe toxic myocarditis. When properly done it is less disturbing than intramuscular injection, as there is no pain. It has the advantage that glucose may be given at the same time to patients who cannot swallow. The largest dose of concentrated antitoxin that can be given intramuscularly is about 40,000 units with each puncture. The best site is the thigh or buttock. The intravenous dose is limited only by the ability of the poisoned circulation to receive it. Anti-scarlet-fever serum was given in addition to three patients suffering from the grave "bull-neck" disease, but with no obvious effect.

Of the eighty-two patients who recovered eight received 100,000 or more units each. In two cases initial doses of 100,000 units on the first day of the disease and 150,000 units on the third day were given; the remaining six had been ill for more than three days before receiving antitoxin. The largest amount used in any case was 648,000 units, which was given to a girl who had been ill for seven days. On the seventh day 50,000 units were given intramuscularly and 250,000 units intravenously. On the ninth day 200,000 and on the tenth day 148,000 units were given intravenously. The patient showed signs of severe myocarditis, the pulse rate was 130–140 for five days, the apex beat moved outwards beyond the anterior axillary line, gallop rhythm was present, the liver was enlarged and tender, and jaundice and albuminuria were present. Recovery was complete.

Brachial Paralysis following Serum

Roger, Mattei, and Paillas (1931) have collected seventy cases of brachial paralysis following serum treatment. Forty followed injection of tetanus antitoxin and only nine injection of diphtheria antitoxin. Allen (1931) has reviewed forty-two reported instances of the neurological complications of serum treatment. Twenty-six followed the use of anti-tetanic serum, whereas four each followed the use of anti-diphtheritic and of anti-streptococcal, and three each the use of anti-pneumococcal and of anti-scarlet-fever serum. Allen divides the cases of paralysis into four groups: radicular, neuritic, polyneuritic, and central.

In one of our patients, a boy of 16 years, treated with 600,000 units of antitoxin, brachial paralysis occurred. On the third day of his illness the fauces were widely covered with membrane, the neck, fauces, and palate were swollen and oedematous, the cervical glands enlarged and tender, and an offensive sanious discharge issued from the nostrils. There were superficial wounds and ulcers on the knees and hands, from which diphtheria bacilli were grown. Eighty thousand units of antitoxin were given intramuscularly and 100,000 units intravenously. On the fifth and sixth days 220,000 and 200,000 units were given respectively. Signs of myocarditis were evident. During the sixth and seventh weeks weakness of the legs and of the external rectus muscle of the left eye, and paralysis of accommodation in both eyes and of the palate, appeared. Weakness of the right upper arm and shoulder-girdle was present, seriously limiting abduction of the right arm. All tendon reflexes were absent, but no loss of sensation or muscular wasting could be detected. Six months later recovery was complete. In this patient there is no obvious reason why the paresis of the upper arm should not have been due to diphtheritic neuritis occurring in an unusual situation. It is not apparent why brachial paralysis following the use of diphtheria antitoxin should be ascribed to the serum rather than to the disease.

Severity of the Disease

As an example of the malignant and fulminating nature of the disease in some instances, we cite the case of a child aged 3½ years, who had been treated two months previously for mild uncomplicated whooping-cough. One morning she complained of sore throat, and was removed immediately to hospital. The temperature was 104° F., pulse 120, and respirations 25; tonsils were swollen and congested, and cervical glands enlarged and tender; no exudate could be seen. Ten thousand units of antitoxin were given intramuscularly. Thirty-six hours later the temperature was 104° F., pulse 156, and respirations 32; the glands were more swollen, there was oedema of the neck, fauces, and uvula, and a patch of exudate less than a threepenny piece on one tonsil. She was restless and looked toxic. Sixty thousand units were given intramuscularly and 140,000 intravenously. She died seven hours later, despite the use of 210,000 units of antitoxin within thirty-six hours of the first appearance of symptoms. Post-mortem examination did not reveal any diphtheritic membrane; there was great oedema of the fauces, glottis, and tissues surrounding the trachea; the lungs were slightly congested; the oesophagus and stomach were normal; the heart muscle was pale, soft, and showed great cloudy swelling, as did also the liver and kidneys. Antitoxin from the supply used in the treatment of this child proved potent to protect guinea-pigs from the virulent diphtheria isolated from her throat.

Of the seven patients who died, two suffered from laryngeal obstruction and were subjected to tracheotomy. One of these died from asphyxia, the other from myocardial failure. Necropsy was done on six of the seven patients who died, and the usual lesions were found. Cloudy swelling of the myocardium, kidneys, and liver were present in all. Two hearts gave striking examples of focal necrosis with areas of small round-celled infiltration scattered through the muscle. A large firmly adherent ante-mortem thrombus was found near the apex of the left ventricle in one case.

Conclusions

The increased case mortality in the Dunedin Hospital during the last three years coincides with the appearance of an exceptionally malignant type of disease.

This type of diphtheria is so little influenced by the usual doses of antitoxin that it is futile to give them.

We believe that the lives of some patients, in desperate straits, have been saved by giving half a million or more units.

We wish to thank Professor D. W. Carmalt-Jones and Professor Frank Fitchett for allowing us access to the patients who were under their care.

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AN UNUSUAL NEISSERIA IN A CASE OF CHRONIC BRONCHITIS*

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In the *British Medical Journal* of February 14th, 1931, Drs. Kirkland and Storer, while describing a case of coryza due to "gonococcal rhinitis," state that "the bacteriological diagnosis is made difficult by the similarity of the *Micrococcus catarrhalis*, which is also Gram-negative and sometimes occurs in pairs, but is never intracellular." This statement,[1] however, is inaccurate, as any of the Neisseria *may* occupy such a position. An example of this is afforded in the present case.

Case Record

A labourer, 58 years old, was seen as an out-patient on January 26th, 1932, complaining of cough with a scanty spit, and steadily increasing muscular weakness, by reason of which he had stopped work. He was well built, well nourished, but of poor muscular tone and posture. The skin was pale and yellowish. Beyond some harshness of breath sounds and slight prolongation of expiration, no abnormal signs were found in the respiratory system. The circulatory, alimentary, nervous, and urinary systems presented no abnormality. The sputum was repeatedly examined for tubercle bacilli, and none were found, but large numbers of

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