A Consideration of Whooping Cough

With Special Reference to
An Experimental Investigation into
The Efficiency of Antibiotic Treatment
of the Disease with
Aureomycin and Chloramphenicol

by

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INTRODUCTION.

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Historical.

The first detailed description of whooping cough, as cited by Major (1945), was by Guillame Baillou, a native of Paris, who described an epidemic which occurred in 1578. He emphasised the severe and often fatal nature of the illness and its ability to affect children of all ages. Prior to that date the disease was popularly known in England as chincough or kincough, but writers do not appear to have recognised it as a specific infectious disease. Sydenham (1679) in his "Opera universa" gave a clear picture of the disease, and named it pertussis (from the Latin per - intensive, and tussis - cough). He pointed out that the disease did not respond to the usual treatments.

In 1682, Thomas Willis emphasised the epidemic character of the disease and wrote, "The plan of treatment which is usual in other varieties of cough is seldom of any use in this, which is the reason why old women and gypsies are consulted more often than doctors."

Dr. Robert Watt (1888) recorded that "Next to the smallpox formerly, and measles now, chin-cough is the most fatal disease to which children are liable." In Aberdeen, according to J.S. Laing, as cited by Goodall (1928), there were 20,425 cases notified in the years 1882-1900: epidemics occurred every two years. In Edinburgh and Glasgow they occurred every three or four years. In 1890, 11½ per cent of the total deaths of children under ten years of age in the city of Glasgow were due to whooping cough.

The search for the causal micro-organism of whooping cough began with the growth of the bacteriological concept of infectious disease, and as far back as 1870, Letzerich described a fungus which he believed to be associated with the disorder.

In 1883, Burger published a paper in which he described, with two woodcuts, the presence of large numbers of small ellipsoidal rods in stained films of the expectoration. The description and illustrations suggest that he actually saw the Haemophilus pertussis.

In 1901, Jochmann and Krause described a small bacillus which they cultured on blood agar, and called the Bacillus pertussis Eppendorf, and this appears to be the first use of the present Latin name of the organism of whooping cough. Credit for the ultimate establishment of Haemophilus pertussis as the causal organism of whooping cough goes to Bordet and Gengou (1906) and a fuller description of their work will be given later.

The Incidence of Whooping Cough.

Whooping cough has a wide distribution in countries with temperate climates. The disease exhibits periodic epidemics, but these tend to occur at less regular and longer intervals than do similar outbreaks of measles (Butler 1947). Females tend to be more often affected than do males, and Roseneau (1935) points out that more females than males have died from the infection.

Unlike the other common infectious diseases of childhood, whooping cough attacks children under six months of age with great frequency. Stocks and Karn (1932) estimated that in four London boroughs 44 per cent of children suffer from infection before reaching five years of age, and 60 per cent before reaching ten years of age. Cockayne (1913) quotes Sir Thomas Watson who described a case where the disease commenced before the child was born. The infant was said to have whooped in the first day of his life. Cockayne described a mild case in a child aged five days whose mother and brother had whooping cough. Phillips (1921) described two infants who sickened with the disease on the 8th and 10th days;

both of these infants whooped before they were 15 days old. My own youngest case was a male child aged 19 days who was admitted from a household with whooping cough. This child had a well-developed paroxysmal cough and whooped on admission. Although whooping cough is essentially a disease of children, adults do not escape and at least one case has been described in a person of 81 years of age.

Epidemiology.

Kohn and Fischer (1947) state that during the year 1941, 3,668 deaths were recorded in the United States of America as being due to whooping cough. In a large New York hospital the case fatality rate for whooping cough during the eight-year period from 1939 to 1946 was equal to or greater than the combined deaths due to measles, scarlet fever and diphtheria.

In London, Stocks and Karn (1932) estimated that the fatality rate for children under one year was 4 per cent, and that the general fatality rate was 1.26 per cent. Butler (1947) compared the fatality rates of whooping cough and measles and pointed out that in England and Wales, since the passing of the Public Health Act in 1875, the annual mortality had fallen for each year from over 400 to about 30 per million of the population. This was not accompanied by any corresponding fall in prevalence of the disease. In Glasgow the general prevalence of the disease has not fallen but the death rate has progressively declined (Logan, 1949). Logan also indicated that there has been an upper age-shift in the incidence of whooping cough but no evidence of a similar age-shift in deaths.

Whooping Cough in Glasgow.

At the beginning of the century, Dr. J.B. Russell (1905), who was the first full-time Medical Officer of Health of the city, wrote:-

"Estimated simply by the number of its victims, whooping cough is by a long way the most formidable infectious disease known to Glasgow. We might probably generalize and say the most formidable infectious disease of industrial cities."

Table 1.

Mortality of the Commoner Infectious Diseases in Glasgow expressed as a Rate per Million of Children under Ten Years.

	Scarlet Fever	Diphtheria and Croup	Whooping Cough	Measles
1860-64	4,724	3,165	6,480	3,663
1865-69	5,860	2,106	5,954	3,687
1870-74	5,732	2,627	5,202	3,376
1875-79	2,631	2,252	5,454	2,351
1880-84	2,942	2,308	5,379	2,942
1885-89	1,777	1,969	4,755	2,536
1890-94	1,478	1,707	4,108	3,956
1895-99	1,019	874	3,830	3,404
1900-04	710	722	3,798	2,247
1905-09	441	957	3,823	3,036
1910-14	721	993	2,535	2,558
1915-19	514	763	2,865	2,583
1920-24	323	683	1,939	2,737
1925-29	218	579	1,720	1,291
1930-34	284	536	1,195	1,353
1935-39	108	715	959	630
1940-44	27	575	484	227
1945-49	14	87	163	98

Table 1 shows the death rate from scarlet fever, diphtheria, whooping cough and measles, calculated against the child population under ten years of age, which existed at the various five-yearly periods since 1890. These figures have been plotted on a logarithmic scale and the resulting chart is shown (Figure 1). During the forty years from 1860 to 1899, the public health service of the city had been developing, and, as a result, the fall in death rates for scarlet fever and diphtheria had been dramatic. In the five year period from 1895-1899, the death rates per million of children under ten years from scarlet fever and diphtheria were 1,019 and 874, and for whooping cough

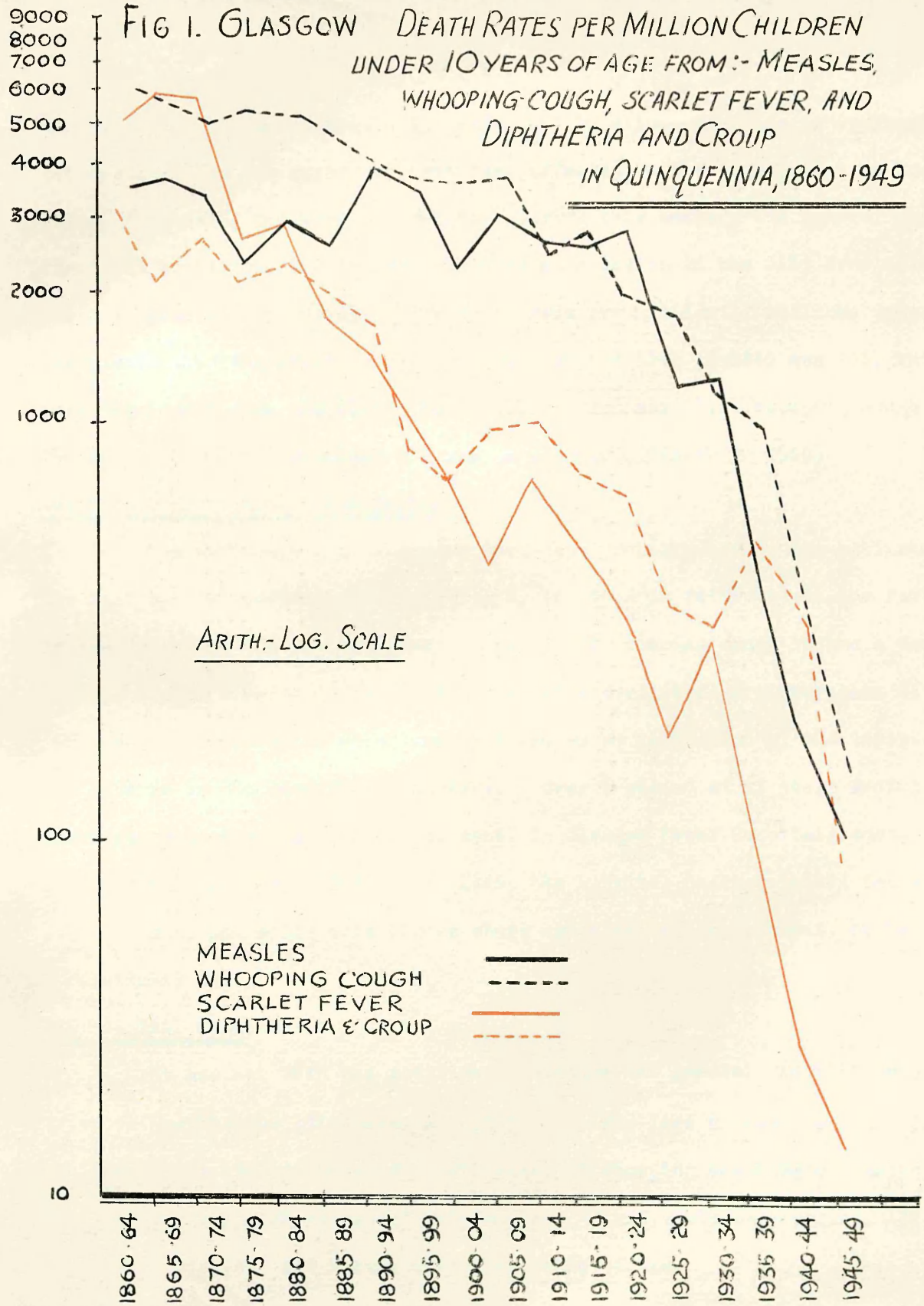


FIG 1. GLASGOW DEATH RATES PER MILLION CHILDREN UNDER 10 YEARS OF AGE FROM :- MEASLES, WHOOPING-COUGH, SCARLET FEVER, AND DIPHTHERIA AND CROUP IN QUINQUENNIA, 1860-1949
9000
8000
7000
6000
5000
4000
3000
2000
1000
100
10
ARITH.-LOG. SCALE
MEASLES
WHOOPING COUGH
SCARLET FEVER
DIPHTHERIA & CROUP
1860-64
1865-69
1870-74
1875-79
1880-84
1885-89
1890-94
1895-99
1900-04
1905-09
1910-14
1915-19
1920-24
1925-29
1930-34
1935-39
1940-44
1945-49

and measles 3,830 and 3,404. A steady fall in all death rates is apparent, but measles does not appear to have been affected to the same extent as scarlet fever, diphtheria and whooping cough. During this century the general downward trend has continued, and in 1950 there were no deaths in the City from either scarlet fever or diphtheria. The death rate per million of children under ten years with whooping cough in the five-year period 1945 to 1949 was 163, which is more formidable than the figure for measles which was 98. Whooping cough remained the most important infectious disease as a cause of death in 1950.

Death Rate in Glasgow Fever Hospitals.

The seriousness of whooping cough has probably been under-estimated in the past by both medical and lay persons, and this is reflected in the fact that it was not until the 1st of January, 1950, that whooping cough became a compulsorily notifiable disease in Scotland. Reliable statistics are therefore difficult to obtain. One factor which can be taken as an indication of the importance of the disease is the hospital death-rate. Over a period of 22 years ending in 1890, there was a death-rate of 18.3 per cent. in Glasgow Fever Hospitals among 5,000 patients treated (Ker, 1909). By 1949, the hospital death-rate had fallen to 5.0 per cent, and while this figure shows considerable improvement, it is still a formidable one.

The Hospital Case.

It has not been the practice in Glasgow for general practitioners to refer to hospital children with whooping cough who live in good homes. During the year, July 1950 to June 1951, 271 cases of whooping cough were treated in Ruchill Hospital, 128 males and 143 females. During the same period, 132 were aged under one year and 9 were over five years of age.

Table 2.

Social Class of 271 Whooping Cough Patients treated in Ruchill Hospital from July 1950 to June 1951 - Divided according to Dismissals and Deaths.

Social Class	Dismissals	Deaths	Total
I	0	0	0
II	4	1	5
III	34	5	39
IV	98	4	102
V	84	3	87
Institutional	38	0	38
All Classes	258	13	271

The majority of patients who were admitted belonged to the Registrar General's social classes IV and V, as is shown in Table 2. No patients who belonged to social class I were admitted during the year, and, generally speaking, only severely ill patients were admitted from social classes II and III.

Table 3.

Possible Reasons for Admission of 271 Whooping Cough Patients treated in Ruchill Hospital in the Year July 1950 - June 1951.

Institutional	38
Critically ill	15
Suspected chest complications.	93
Concurrent bronchopneumonia ..	42
Overcrowded home conditions ..	183

The possible reasons for admission of the 271 whooping cough patients are shown in Table 3. Thirty-eight of the cases came from institutions, 9 of these were admitted from wards in general hospitals, and 29 from residential nurseries and children's homes. Fifteen were critically ill, and of these 13

died. Forty-two patients were suffering from concurrent bronchopneumonia, and 93 were suspected of having chest complications. Atelectasis, which persisted longer than three weeks, was noted in 28 patients, and 12 of these were discharged with persistent radiological lesions and were referred to chest clinics as out-patients. One hundred and eighty-three of the patients came from overcrowded homes, and a few of these were undernourished and in a neglected condition. Forty-six patients had been ill for longer than three weeks prior to admission to hospital, and for this reason they were unsuitable for inclusion in any trial of a new treatment for the disease.

The average period of residence in hospital for whooping cough patients in Glasgow fever hospitals during the year 1950 was 42 days. This figure was considerably greater than the average period of residence for measles cases, which was 18 days and scarlet fever which was 22 days.

During the year, July 1950 until June 1951, there were 13 deaths in the acute stage of the disease. Seven of the deaths were in females and six in males. The ages of the fatal cases ranged from six weeks to three years, seven patients being under one year of age, five in the age group 1-2 years, and one aged three years.

Table 4.

Associated Cause of Death in 13 Whooping Cough Patients.

Bronchopneumonia	4
Atelectasis	3
Atelectasis and Bronchopneumonia .	1
Convulsions	4
Emphysema of Lungs, Interstitial Emphysema of Mediastinum and Neck	1
Total	13

Chest complications, bronchopneumonia and atelectasis caused death in eight patients, as is shown in Table 4. Convulsions caused death in a further four patients. Eleven of the patients came from good homes, and two from overcrowded home conditions. All except one of the patients appeared to be well-nourished. On the average, patients had been ill for 14.5 days before admission, and the average residence in hospital before death was 8.8 days. Five children, three with convulsions and two with pneumonia, died within 48 hours of admission to hospital.

A female child, aged 9 months, who had a history of spasmodic cough with vomiting for four weeks, was admitted because of difficulty in breathing for 24 hours before admission. On examination there was a tense swelling of the right cheek and both sides of neck with marked crepitus. The child died four days after admission and post-mortem examination revealed air bubbles of varying size in the subcutaneous tissues overlying the sternum and the fat surrounding all structures in the anterior and posterior mediastinum. All lung surfaces showed numerous emphysematous bullae of varying sizes. The histological appearances of the lungs suggested that death was due to a mechanical cause rather than to pyogenic obstruction.

The death of four patients from nervous complications was extremely distressing. For example, a three year old female child sickened three weeks and developed a spasmodic cough with whoop about two weeks before admission. The history obtained from the parents and general practitioner suggested that the case was one of moderate severity. The child had been ambulant, but 48 hours before admission it was noted that she was not well. Six hours before admission the child had two convulsions lasting 10 minutes and 35 minutes. On admission

the child was convulsing, and despite energetic treatment this continued until death 18 hours later. Post-mortem examination failed to reveal the cause of death, as is usual in this type of fatality.

Patients with bronchopneumonia were given treatment with sulphadiazine or penicillin, and in severe cases both drugs were used simultaneously. Oxygen was administered to the more severely ill patients, and special nurses were provided when necessary. Despite this, eight patients died from chest complications during the year from July 1950 to June 1951.

Consideration of the facts and figures quoted suggested that further research into the nature and treatment of whooping cough was desirable for it became obvious that the need for improved methods of handling the disease was clamant. It was with the hope of improving the standard methods of treatment that the investigation about to be described was carried out.

CHAPTER 2.

THE DIAGNOSIS OF WHOOPING COUGH.

DESCRIPTION AND ASSESSMENT OF METHODS.

Because whooping cough is a naturally variable disease, it is not surprising that confirmation of the diagnosis often presents difficulty. As the illness lasts for a considerable period, and the onset is gradual and insidious, it seems reasonable to assume that the earlier the diagnosis can be confirmed and treatment commenced, the greater will be the likelihood of success. From an epidemiological point of view the subject of whooping cough is probably in a highly infectious state during the catarrhal stage, and early isolation of the patient would limit the spread of infection. The methods used for the diagnosis will now be discussed. They may be summarised as follows:-

1. Clinical signs.
2. Isolation of the causative organism.
3. Complement fixation tests.
4. Intradermal sensitivity tests.
5. Haematological tests.

Clinical Signs.

It is not proposed to describe the clinical picture of whooping cough in detail. The most characteristic clinical sign, the whoop, is heard late in the disease, and in some cases may not be heard at all. Clinical signs are of little value in early diagnosis. During an epidemic the combination of the early signs of whooping cough along with a history of contact with a previously known case is an invaluable guide to diagnosis. Whooping cough is different from the other common infectious diseases of childhood where the onset is acute. Clinical signs alone often do not indicate the specific diagnosis.

Isolation of the Causative Organism.

The Causative Organism. Infection with Haemophilus pertussis is now generally accepted as being the cause of whooping cough. In 1900 it was first seen by Bordet and Gengou in the Pasteur Institute in Brussels, but it was not until

1906 that they were able to cultivate it from a plug of mucus obtained from the bronchial tree of a patient with whooping cough. Difficulty was experienced in obtaining a primary culture. For this purpose a medium consisting of a glycerin gelatin maceration of potatoes with an equal quantity of human blood or rabbits' blood was used. After obtaining a primary growth the organism was maintained on ascitic gelatin. They described the organism as being gram negative, and ovoid, micrococcal, or elongated in shape. The medium originally used for the isolation of the bacillus of Bordet and Gengou, now known as the Haemophilus pertussis, is still, with certain modifications, used today.

In 1916, Chievitz and Meyer, working in Copenhagen, confirmed the work of Bordet and Gengou and first described the cough-plate method of diagnosis. In a foundling home Meyer carried out tests on seven children who were suspected of being in the catarrhal stage of the disease. Each child was made to cough on to medium contained in a petri dish held ten centimetres from the mouth. After incubation, colonies of Haemophilus pertussis were isolated from five of the seven plates. They pointed out the great value of this method in early diagnosis of the disease, but it was not to be put into general use for some years.

Further experimental work to confirm that Haemophilus pertussis was the sole cause of whooping cough was carried out by Sauer and Hambrecht in America in 1929. Paroxysmal cough developed in five healthy young monkeys one to three weeks after Haemophilus pertussis had been introduced into the larynx. After death the bacteria was recovered from the throat, larynx, trachea and lungs. Animals which recovered from the disease were immune to subsequent injections of Haemophilus pertussis. Further evidence to support the theory was supplied in 1933 when the Macdonalds introduced the organism into the nose and throat of each of their four

sons. Two of the boys, who had five months previously been inoculated with a specially prepared vaccine, did not develop the disease; whereas the two who had not been so treated developed clinical whooping cough which was confirmed bacteriologically and haematologically.

The Cultural Phases of Haemophilus Pertussis. Leslie and Gardner (1931) pointed out that after isolation from the human subject the Haemophilus pertussis tends to pass through a series of antigenically distinct cultural phases. The first and second phases are smooth, and the third and fourth are rough. Guinea pig experiments suggested that the more toxic phase 1 was solely responsible for conferring active immunity.

The Cough-Plate Method of Isolation of Haemophilus Pertussis. In Oxford, in 1932, Gardner and Leslie using the cough-plate method reported that 75 per cent of 82 patients with whooping cough were diagnosed in the early stages of the disease. They were aided in their work by the method, previously described by Sugare and Macleod (1929), of cutting spreading colonies out of the medium. One sub-clinical case was diagnosed bacteriologically. In Denmark the following year this important diagnostic method was underlined by Kristensen (1933), who published the results of 15 years' experience. Missed and atypical cases, especially in adults, were thought to be an important factor in the spread of the disease.

By 1937 the Danes had a bacteriological diagnostic station which was widely used. Madsen (1937) claimed that in the catarrhal stage of the disease, Haemophilus pertussis could be isolated from 74 per cent of whooping cough patients. The greatest difficulties were the delay due to the slow growth of Haemophilus pertussis and to the inimical presence of other organisms. Straker and Westwater (1937) showed similar results and suggested that the cough-plate method should be used for routine diagnosis of whooping cough in this country.

The Use of Penicillin with the Medium. In 1929, Fleming noted that penicillin had great inhibiting powers on the growth of gram-positive bacilli. This was used by Maclean in 1937, when he carried out a controlled experiment by spreading six to eight drops of strong penicillin over half the medium in the plate, the other half being left untouched. Fifty cough-plates were exposed and it was found that 47 were positive for Haemophilus pertussis in the treated portions and 33 were positive in the untreated portions. This work was confirmed by Bradford et al. (1946) who used the nasopharyngeal swab method for culture.

In 1946, working in Australia, Anderson was first to incorporate the penicillin in Bordet-Gengou medium. She isolated Haemophilus pertussis from 79 out of 154 unselected whooping cough patients, as against 39 positive when no penicillin was incorporated in the medium.

Swab Techniques used for the Isolation of Haemophilus Pertussis. For use in general practice, the cough-plate method has obviously serious disadvantages in that it is difficult to obtain fresh medium and to get satisfactory exposure at the correct time. Transportation to the laboratory is also a problem in out-patient work. To obviate these difficulties, Maclean (1937) used a pharyngeal swab and claimed to isolate the organism from 75-80 per cent of whooping cough patients. In London, Cruickshank (1944) carried out a comparative trial of the cough-plate and post-nasal swab methods. Sixty-seven positive cultures were obtained from 250 patients, but it was pointed out that many cases were admitted to hospital late in the illness. The results of the two methods were roughly comparable, but for children under two years of age the post-nasal swab appeared to be the method of choice. Tarr (1946) described a modified post-nasal swab for use in the culture of the Haemophilus pertussis. The swab used was claimed to be of spedial value for young children, but it was never put into general use.

In these experiments the posterior wall of the nasopharynx was swabbed by way of the mouth. Bradford and Slavin (1940) took nasopharyngeal swabs by passing a flexible copper wire, with a small piece of cotton wool on the end, through the nose until it touched the posterior wall of the nasopharynx (a pernasal swab method). In comparing the results of 40 primary cultures from 22 whooping cough patients there were 22 positive nasopharyngeal swabs, 10 positive cough-plates and 5 positive throat cultures. In only three cases were the cough-plate cultures positive when the nasopharyngeal swab was negative. They also found that there was a more profuse growth of Haemophilus pertussis on the medium and a minimal amount of secondary invaders when the nasopharyngeal method was employed. The same workers (Brooks et al., 1942) published a larger series of 438 cases in which 52 per cent were positive by the nasopharyngeal method and 27 per cent were positive using the cough-plate method. These findings were confirmed by Saito et al. (1942) and Bullowa et al. (1944).

The nasopharyngeal swab method, used for the culture of Haemophilus pertussis, appears cumbersome and uncomfortable for the patients. In 1948, Cockburn and Holt described a pernasal swab which was made from an extremely fine nickel chrome wire. This swab would be passed through the nostril to the posterior wall of the nasopharynx, and caused the minimum of upset to the patient. The method was used in the recent Medical Research Council trial (1953). Cockburn and Holt took simultaneous swabs by pernasal and postnasal methods, and positive results were obtained on 30 occasions. In 23 instances both swabs were positive and in 7 the pernasal swab only was positive. They also proved that there was a greatly reduced contamination of plates inoculated from pernasal swabs. The pernasal swab is apparently more reliable for the isolation of Haemophilus pertussis than the postnasal swab. It was, however,

pointed out that sometimes a negative result is obtained even in the early stages of the disease.

Complement Fixation Tests.

In their original work, Bordet and Gengou (1906) noted that serum from cured cases of whooping cough showed fixation of complement in the presence of antigen prepared from a pure culture of Haemophilus pertussis. This test was not positive until the convalescent stage of the disease. Like all specific antibodies, however, their presence only proved that the subject had recently been under the stimulus of the specific antigen and not that he was suffering from infection at the time of testing. Donald (1938) was of the opinion that the test was of value in retrospective diagnosis, but it was not positive until the third or fourth week or later. In practice this test is rarely used, and its chief value lies in these cases where retrospective diagnosis is essential.

Intradermal Sensitivity Tests.

The demonstration of specific antibodies to the causal organism by means of a skin test has been attempted from time to time. In 1937, Paton carried out an extensive experiment in Belvidere Hospital, Glasgow. An intradermal injection of whole or disrupted Haemophilus pertussis was used in a controlled experiment. It was found that the intradermal test failed to give a specific result, and that a positive result was obtained in some of the patients in the control group in whom there was no history of their having had whooping cough. Donald (1938) partly repeated the experiment, but his results were unreliable and this method of diagnosis was abandoned.

Using a endotoxin of Haemophilus pertussis, Thompson (1938) indicated that there was some parallel between a positive reaction and a history of having had

whooping cough. There were, however, about 30 per cent of apparently non-specific reactors. The test is of no value in the early diagnosis of whooping cough.

Haematological Tests.

In many cases of whooping cough a raised leucocyte count with a relative or absolute lymphocytosis is present in the late catarrhal stage, and this persists into the paroxysmal stage. The erythocyte sedimentation rate is seldom raised in normal cases.

Blood Counts. In 1922, Bourne and Scott reported a case of whooping cough in a female child, aged one year and nine months, in which there was a leucocyte count of 176,000 per cubic millimetre (116,000 lymphocytes per cubic millimetre) in the seventeenth day of illness. The count fell to 45,000 per cubic millimetre on the forty-first day of illness. Seitz (1925) described two cases of leucocyte counts over 150,000 per cubic millimetre in children with whooping cough.

Begg and Coveney (1935) reported on the blood findings in 65 uncomplicated whooping cough patients, most of whom were in the late catarrhal and early paroxysmal stage of the illness. Total and differential leucocyte counts were performed on admission to hospital and during early convalescence, and the figures obtained were compared with the normal for the particular age group. There was an increase in the number of leucocytes in every case, but lymphocytosis was only present in 77 per cent of patients. In 35 per cent of the patients, lymphocytosis was well-marked, and in 23 per cent there was no absolute lymphocytosis. The authors were of the opinion that blood changes were maximal early in the disease. Gardner (1936) pointed out that lymphocytosis is not present in the early catarrhal stage, and this was confirmed by Donald in 1938.

Erythrocyte Sedimentation Rate. In 1936, Gold and Bell described a diagnostic trial consisting of a suspicious cough along with a retarded erythrocyte

sedimentation rate and a lymphocytosis which they considered to be pathognomonic of whooping cough. Employing the Westergren method, Donald (1938) measured the erythrocyte sedimentation rates of 95 uncomplicated cases of whooping cough. The sedimentation rates were retarded or normal in the second and third weeks of illness, and showed slight acceleration later in the disease. In the control group of 24 patients with acute bronchitis, 29 per cent also showed a normal or retarded erythrocyte sedimentation rate. This test is, therefore, of little value in itself. My experience in a whooping cough ward has been that few patients were old enough to allow me to obtain a sufficient quantity of blood for the test.

Summary.

The methods of diagnosis of whooping cough have been discussed. Clinical signs alone are of little value in early diagnosis, and if relied upon solely, many mild and subclinical cases may be missed. Early diagnosis can only be made with certainty when the causal organism, now accepted as being the Haemophilus pertussis, is isolated. The method of choice is the pernasal swab cultured on Bordet-Gengou medium containing a suitable quantity of penicillin to limit the growth of secondary invading organisms. In many instances a raised leucocyte count with a relative and absolute lymphocytosis is present from the late catarrhal stage. It is a useful pointer to the diagnosis especially when there are suspicious clinical signs. Erythrocyte sedimentation rates are of doubtful value in diagnosis. For retrospective diagnosis, complement fixation tests may be used, but skin tests are of no value.

CHAPTER 3.

THE TREATMENT OF WHOOPING COUGH BY ANTIBIOTICS.

Owing to the lack of suitable therapy and to its distressing nature, few diseases have been subjected to more varied modes of treatment than whooping cough. Lapin (1943) quotes one writer as stating that he had collected and listed 400 drugs and therapeutic measures said to be beneficial. In 1903, Sobel advocated the treatment of the paroxysmal cough by pulling the lower jaw downwards and forwards, and listed the following procedures and drugs as being in use at the time of his writing:-

> "Antispasmodics, narcotics, nervines, anaesthetics, astringents, inhalations, local applications, intubation, tracheotomy, vaccination, formalin, diphtheritic serum, counter irritation over the pneumogastrium, compressed air, carbonic acid gas per rectum, suggestive therapy and ozone."

These examples illustrate the wide range of treatments, local and otherwise, that physicians have invented in their endeavour to find a solution to the problem of the treatment of whooping cough. Since the time of Sobel's writing, many other forms of therapy have been tried, but as this thesis is concerned mainly with the antibiotic treatment of whooping cough, only the literature relevant to this aspect will be discussed.

Experimental Work.

It was soon discovered that penicillin and the sulphonamides had no effect on the growth of Haemophilus pertussis, nevertheless, they were found to be of great value in the treatment of many of the complications of whooping cough. As a result each antibiotic, as it appeared, was subjected to an experimental evaluation in order to assess whether or not it was likely to be of use in the treatment of the disease.

In 1950, Wells et al. carried out in vitro tests for sensitivities on recently isolated strains of Haemophilus pertussis with the following antibiotics:-

Penicillin, Streptomycin, Bactracin, Polymyxin B, Polymyxin D, Aureomycin, Chloromycetin, Neomycin, and Terramycin.

The strains used were obtained from nasopharyngeal cultures from active cases of whooping cough. After incubation for 72 hours the strains were subcultured on to plates containing twofold dilutions of each antibiotic used. After testing 31 strains of Haemophilus pertussis it was concluded that polymyxin was by far the most effective of the antibiotics. Chloramphenicol, aureomycin and terramycin appeared to be of moderate value, and penicillin, streptomycin, neomycin and bactracin were of no value in preventing the growth of Haemophilus pertussis.

In 1946 the Shaffers in New Orleans, confirming the work of Gallavan and Goodpasture (1937), suggested that the susceptability of chick embryos to Haemophilus pertussis might be of use in the evaluation of antibiotic preparations against the organism. The method was applied in 1950 by Jackson, Barnes and Finland who compared the action of seven antibiotics against Haemophilus pertussis infection in chick embryos. It was found that penicillin, polymyxin B, streptomycin, neomycin, aureomycin, chloramphenicol and terramycin in suitable doses prolonged the life of the embryos.

Hegerty and his co-workers (1945) showed that streptomycin, exhibited in vitro, had bacteriostatic activity against Haemophilus pertussis, and that mice treated with intranasal streptomycin survived twice as long as control mice who were not so treated. This work was confirmed by Bradford and Day (1949) who showed that aureomycin and polymyxin were also effective against infection in mice, and they considered aureomycin to be more effective than streptomycin. Bell, Pitman and Olson (1949) confirmed the value of aureomycin in treating experimental pertussis infection and noted that: "A treatment regime of small doses given at

frequent intervals over a period of several days was more effective than larger doses given singly or at infrequent intervals for a few days." A small clinical trial of aureomycin in known cases was carried out and favourable impressions were reported.

Results of Clinical Trials of Antibiotics in Whooping Cough.

Polymyxin. Swift (1948) carried out an uncontrolled experiment in which ten patients with whooping cough were treated with polymyxin, and it was claimed that in all cases there was definite improvement within 24 hours. On the other hand, Kaplan (1949), in New York, who treated 84 children suffering from whooping cough, considered that polymyxin had no effect on the course of the disease. In 1951, Banks treated 17 bacteriologically confirmed uncomplicated whooping cough patients, all in the 8th and 16th days of illness, with polymyxin. The drug appeared to be effective but was too toxic for general use. This view of the drug's toxicity was generally accepted and production of polymyxin was stopped. However, recently the use of polymyxin in modified doses has been found to have a greater margin of safety.

Streptomycin. In 1948, Leichenger and Schultz conducted a well-controlled trial in which 16 early cases of whooping cough were treated with streptomycin. The daily dose of one gram was administered to eight patients by the aerosol route, to eight patients by intramuscular injection, and there were eight controls. All the patients were in the same ward and careful note was kept of the number of paroxysms and vomits in each 24-hour period. It was considered that the aerosol route of administration was the method of choice, and they concluded that streptomycin appeared to be an effective therapeutic agent for whooping cough. A larger series of 29 whooping cough patients was reported by Wannamaker et al. (1949) who

administered streptomycin by intranasal drops, aerosol mist, and intramuscular injection. Twenty-one children, who were selected mild cases, acted as controls. It was discovered that despite satisfactory blood levels, streptomycin did not influence the presence of Haemophilus pertussis in the nasopharynx. They concluded, however, that aerosol and intramuscular therapy with streptomycin favourably influenced the course of the disease. Unfortunately, only clinical impressions were used in assessing the course of the illness and the control patients were not of similar severity to those treated. Later, the same team (Shepard et al., 1949) treated 64 whooping cough patients by combined aerosol and intramuscular methods but concluded that there was no advantage to be gained in combining the methods of administration.

In London, Schwabacher, Wilkinson and Karron (1949) reported a small series of 17 patients in which, despite satisfactory blood streptomycin levels, no beneficial results were obtained as a result of streptomycin therapy. They suggested that resistant strains of Haemophilus pertussis might have developed. Gordon and Almaden (1949) reported a definite and rapid improvement in 24 severe cases of whooping cough treated with streptomycin, and a statistically significant reduction in the fatality rate in the 24 treated patients as compared with 28 control patients. These rather unusual results have not been confirmed.

With the discovery of aureomycin and chloramphenicol, streptomycin therapy was discontinued without its value in whooping cough ever having been satisfactorily assessed.

Aureomycin. Aureomycin hydrochloride was first described by Duggar in 1948. Following the work of Bell at al. (1949), Miller and Ross (1950) of the United States Army Medical Corps reported on the aureomycin treatment of severe

whooping cough in six children. They employed a dosage schedule of 350 milligrams of aureomycin per kilogram of body weight per day for 8 to 10 days. Favourable impressions were recorded.

In 1950, Chang and his colleagues, in Boston, treated 22 bacteriologically confirmed cases of whooping cough with aureomycin. The dose varied from 60 to 100 milligrams of aureomycin per kilogram of body weight each day, and treatment was continued for five days in the first instance. Relapses were reported in three patients who were given a further course of treatment. Controls were used but these were not taken in strict rotation. In the treated patients the frequency and intensity of the paroxysmal cough began to decrease after three days, and the duration of cough was reduced from an average of 30.3 days in the control group to 21.7 days in the treated group. There was also a more favourable response in the treated patients as regards the numbers of paroxysms per day. This trial was well planned, but it is unfortunate that when recording their impressions the observers knew the patients who were receiving treatment and those who acted as controls, thereby introducing a possible element of prejudice.

Abboud et al. (1951), in Egypt, treated 53 selected whooping cough patients with aureomycin and recorded favourable results. There was no adequate control and the criteria used for assessing progress were of doubtful value. Similar unreliable impressions were reported from Germany when 47 cases of whooping cough were successfully treated by Hassleman-Kahlert (1952).

Wehrle and Lepper (1951) reported on the treatment of 137 cases of whooping cough with aureomycin. They did not consider that the drug had any effect in altering the course of the disease. There was, however, a lower incidence of secondary complications in the treated patients compared with a control group,

and a marked decrease in the duration of positive nasopharyngeal cultures was noted in the patients treated.

First reports on the value of aureomycin in the treatment of whooping cough are, therefore, conflicting. Although treatment with the drug appears to cause the disappearance of the Haemophilus pertussis from the nasopharynx, there is not always parallel clinical improvement.

Chloramphenicol. The biological properties of chloramphenicol were described for the first time in 1948 by Smith and his co-workers in Detroit. When tested against Haemophilus pertussis, the drug was found to prevent its growth on rabbits' blood in doses which were non-toxic to animal (McLæn et al., 1949).

In a letter to the editor of the Lancet on 24th September, 1949, Dr. D.P. Degenherdt described an infant suffering from whooping cough who was treated with chloramphenicol, and he observed that there was dramatic improvement. Payne et al. (1949), working in Bolivia where the death rate from whooping cough is very high,also reported on the value of chloramphenicol. Fifty children, all bacteriologically confirmed as suffering from whooping cough, were given chloramphenicol, and it was claimed that there was freedom from symptoms in approximately four days. The extremely rapid decrease in the paroxysmal cough in this series has not been confirmed. One case relapsed after the cessation of treatment. In a series of five infants suffering from severe whooping cough, Macrae (1950) reported dramatic improvement as a result of chloramphenicol therapy. Khalil and Abdin (1950) treated with chloramphenicol 25 early cases of whooping cough. No controls were used but the clinical impressions of the therapy were favourable.

Observations by Gray (1950a) have produced evidence that chloramphenicol depresses the cough count and limits the course of whooping cough regardless of

the stage at which administration is begun. He carried out a well-controlled experiment on out-patients. The patients were treated at home, and the mothers were asked to keep a record of the number of paroxysmal coughs in each 24-hour period. Treatment was unselected and alternate cases were given a capsule containing an inert drug. There was a marked reduction in the cough count in the 29 patients treated with chloramphenicol as distinct from the control group. The beneficial effect of the drug was marked in children treated within 14 days of the onset, but appeared to be of value in later cases as well. Gray carried out careful bacteriological examinations on both groups, and it was discovered that chloramphenicol sterilises the mucous surfaces of the upper respiratory tract. It was indicated that massive bacterial death occurred within an hour of a single dose and that the normal flora did not return for two to three days. In a second paper, Gray (1950b) described the successful treatment of 21 cases of whooping cough with chloramphenicol, in which strict diagnostic criteria were enforced in all cases admitted for trial. Gray advocated a dose of 100 milligram per kilogram of body weight followed by two maintenance doses, depending on age, at eight hourly intervals.

The result of a reasonably large trial was reported by Lassen and Grandjean from Copenhagen in 1951. A series of 100 whooping cough patients, 80 per cent of whom were bacteriologically proven, were treated with chloramphenicol. Progress was assessed by the frequency of the paroxysmal cough and the bacteriological findings. The course of treatment lasted for five days, and all patients improved during the treatment period. Contrary to Gray's findings, seven patients were shown to have Haemophilus pertussis in the nasopharynx after completion of the course of treatment. After a second course of treatment, two of these patients still had the

organism in the nasopharynx. Unfortunately, no controls were used, but it was thought that chloramphenicol was of value in the treatment of all stages of the disease.

Comparative Antibiotic Studies. In 1950, Hoyne and Brown indicated that in the treatment of whooping cough, chloramphenicol was better than aureomycin, and that aureomycin was better than streptomycin, which was considered to be of little value. Hazen et al. (1951) treated 150 early whooping cough patients, all bacteriologically confirmed, with penicillin, aureomycin, chloramphenicol and terramycin. Strict rotation of the drugs was used for the patients admitted to the trial. The penicillin group acted as a control, and this was an attempt to exclude the effect of the other drugs in causing improvement by influencing secondary bacterial invaders. The results were assessed by the average daily number of paroxysms, their severity, and the total duration of the paroxysmal cough. A better response was noted in patients treated with aureomycin, chloramphenicol and terramycin than in those who received penicillin. Weinstein et al. (1951) did not confirm these findings in 80 treated cases. They indicated that aureomycin, chloramphenicol and terramycin had little or no effect in reducing the frequency or severity of the cough in the paroxysmal stage of the disease. Aureomycin and chloramphenicol were almost equally effective in eradication of Haemophilus pertussis from the upper respiratory tract, but the incidence of secondary bacterial invaders was not appreciably reduced.

In a well-organised trial, Booher et al. (1951) reported that the treatment of 111 uncomplicated cases of whooping cough, aureomycin, chloramphenicol and terramycin appeared to be equally effective, but the results were not so good as those obtained by other workers. Gray (1950b) had a similar experience in treating

whooping cough out-patients with aureomycin and chloramphenicol.

Conclusions.

As far back as 1909 Dr. J. Freeman published his experience in the treatment of whooping cough with a vaccine prepared from Haemophilus pertussis. A well-controlled trial was carried out, but after the first month he discovered that his opinion as to progress had been unconsciously biased in favour of the patients receiving vaccine. He concluded:-

> "When a doctor reports that he has a drug which has proved to be of distinct benefit, he should be asked, 'In how many cases have you tried it? Did you have a system of controls? and did you have a colleague to report who did not know which of the cases were controls'? "

Since that time Dr. Freeman's article has often been quoted, but few workers have attained those high principles when testing the efficacy of a new treatment in whooping cough. In the antibiotic treatment of the disease, I can find no instance of an author who was ignorant of the treatment being received when he made his observations. As has been pointed out, in many trials no controls were used, and in many instances the number of patients treated was few. These factors have no doubt been responsible for the conflicting reports in the literature. In 1950 there was obviously need for a well-controlled large-scale trial of aureomycin and chloramphenicol in the treatment of whooping cough.

CHAPTER 4.

A CLINICAL TRIAL OF ANTIBIOTIC TREATMENT OF WHOOPING COUGH ORGANISED BY THE MEDICAL RESEARCH COUNCIL, WITH DESCRIPTION OF THE METHODS EMPLOYED IN A GLASGOW FEVER HOSPITAL (RUCHILL HOSPITAL).

In December, 1949, a working party was formed by the Antibiotics Clinical Trials (Non-Tuberculous Conditions) Committee of the Medical Research Council to consider the problem of the treatment of whooping cough by the newer antibiotics. Glowing reports of the effectiveness of chloramphenicol and aureomycin, both of which were at that time in short supply, had been received, and it was thought advisable to give some guidance to medical practitioners as to the value of these drugs in the treatment of whooping cough. In order to obtain a sufficient number of cases to prove the effectiveness or otherwise of the drugs, there was organised a clinical trial which could be carried out simultaneously at various centres throughout the country. The working party consisted of a bacteriologist who acted as chairman, a statistician who acted as secretary, and physicians from eight infectious diseases hospitals. Dr. Thomas Anderson represented Glasgow and I was privileged in being asked to organise and carry out the clinical trial of the drugs at Ruchill Hospital.

As has been pointed out in a previous chapter, there are many factors which influence the course of whooping cough, which is a naturally variable disease, and this makes the criteria for assessing progress difficult to evaluate. As a result, the working party fully appreciated the need for a strictly controlled trial and that it was necessary for the observer, who was charting the progress, to be ignorant of the treatment which the patient was receiving. The trial was so organised that there should be uniformity at the various centres, and the results when collected were to be analysed centrally.

Organisation of the Antibiotic Trial.

Cases admitted to the Trial. There was no selection of patients, and on admission an assessment was made as to their suitability or otherwise for the trial.

The following were excluded:-

(a) Patients over five years of age, because previous experience had suggested that there would not be sufficient numbers in this age group from which to draw accurate conclusions.

(b) Patients in whom the illness had lasted more than three weeks from the onset of the cough. It seemed unlikely that any treatment would be effective in treating such late cases, although many were complicated and required treatment by antibiotics.

(c) Complicated cases who urgently required treatment by another antibiotic were excluded as it would have been impossible to evaluate the part played by the trial drug in the course of the disease.

(d) Patients who had received chloramphenicol or aureomycin prior to admission.

On admission the patient's name was entered in an 'admission register' and the suitability or otherwise for trial noted (Figure 2). If the case was unsuitable, the reason for exclusion was recorded and, therefore, it was possible to calculate the percentage of admitted cases which were suitable for trial.

Treatment Register. Nine treatment letters denoting the various drugs in the trial were employed. A treatment register, copies of which are shown in Figure 3, consisting of columns which divided the patients into six groups according to age and sex, was provided. The nine treatment letters were arranged at random on the left-hand side of each column, and suitable cases were divided into male and female and into the following age groups:- Under 1 year, 1-3 years and 3-5 years. The name of a suitable case was entered in the first vacant space in the appropriate column, and there the name appeared opposite one of the treatment letters. The treatment was, therefore, unselected.

Figure 2.

PERTUSSIS

ADMISSION REGISTER

DATE COMMENCED .....

Name	Sex	Age	Suitable for Trial (enter "Yes" or "No")	If unsuitable give reason here

Figure 3.

WHOOPING COUGH - TREATMENT REGISTER.

MALES

AGE GROUP								
0-11 MONTHS (Dose: 0.5 G. Twice Daily for 7 Days)			12-35 MONTHS (Dose: 0.75 G. Twice Daily for 7 Days)			36-59 MONTHS (Dose: 1.0 G. Twice Daily for 7 Days)		
No.	Treatment	Name	No.	Treatment	Name	No.	Treatment	Name
1	A		19	B		37	C	
2	B		20	C		38	A	
3	C		21	A		39	B	
4	D		22	E		40	F	
5	E		23	F		41	E	
6	F		24	D		42	D	
7	G		25	H		43	K	
8	H		26	K		44	G	
9	K		27	G		45	H	
10	A		28	B		46	C	
11	B		29	C		47	A	
12	C		30	A		48	B	
13	D		31	E		49	F	
14	E		32	F		50	E	
15	F		33	D		51	D	
16	G		34	H		52	K	
17	H		35	K		53	G	
18	K		36	G		54	H	

Figure 3[a].

WHOOPING COUGH - TREATMENT REGISTER.

FEMALES

AGE GROUP								
0-11 MONTHS (Dose: 0.5 G. Twice Daily for 7 Days)			12-35 MONTHS (Dose: 0.75 G. Twice Daily for 7 Days)			36-59 MONTHS (Dose: 1.0 G. Twice Daily for 7 Days)		
No.	Treatment	Name	No.	Treatment	Name	No.	Treatment	Name
55	H		73	G		91	K	
56	G		74	K		92	H	
57	K		75	H		93	G	
58	D		76	D		94	F	
59	E		77	F		95	E	
60	F		78	E		96	D	
61	B		79	A		97	C	
62	A		80	C		98	B	
63	C		81	B		99	A	
64	H		82	G		100	K	
65	G		83	K		101	H	
66	K		84	H		102	G	
67	D		85	D		103	F	
68	E		86	F		104	E	
69	F		87	E		105	D	
70	B		88	A		106	C	
71	A		89	C		107	B	
72	C		90	B		108	A	

The Drugs. Aureomycin, chloramphenicol and an inert control substance were dispensed in cachets containing 250 milligrams. A mixture of lactose and quinine was used as the control substance, and half the control cachets contained yellow powder to resemble chloramphenicol. The cachets were supplied in containers labelled by the same letters as these on the treatment register, and the patient was given treatment from the container in which his or her treatment letter appeared. Although nine letters were used, three of these denoted the same drugs, thus lessening the danger of a drug being identified by any particular letter. The identity of the drugs was not revealed to us at Ruchill until the trial had been completed.

Dosage and Duration of Treatment. The dosage varied according to the age of the patient, and in all cases treatment was continued for seven days. The following dosage was employed:-

(a) Children 0-1 year of age - Gram. 0.5 twice daily.

(b) Children 1-3 years of age - Gram. 0.75 twice daily.

(c) Children 3-5 years of age - Gram. 1.0 twice daily.

Record Cards. A record card, a specimen of which is shown in Figure 4, was provided for each case. There were sections for notes on the following aspects:-

(a) History of Contact: History of contact with a known case of whooping cough, inside or outside of the home, and the reason for the belief that the primary case was one of whooping cough was obtained from the parents soon after the child's admission to hospital.

(b) History of Onset of Illness. Dates of onset of the earliest symptom, cough, paroxysmal cough, whooping, vomiting and convulsions, if present, were also supplied by the parents.

ANTIBIOTIC TREATMENT OF PERTUSSIS

CASE RECORD SHEET

Hospital .....

Sex .....

Age Group .....

Treatment Letter .....

(Complete on discharge)

Child's Name ..... Sex..... Age.....
(in years and months)

Date of admission ..... Treatment [ ] Letter

History of Contact:

1. Is the child a known contact (encircle appropriately) YES NO

2. If a known contact (a) What is the evidence of pertussis in the infecting (primary) case? (e.g., "diagnosed by general practitioner", "is whooping and vomiting", "is swab +ve", etc.).

II

(b) What was the nature of exposure? (indicate appropriately).

1. The children live in the same household.

2. They are in different households but were in contact as follows:

Previous History: 1. Date of onset of (a) Earliest symptoms (catarrh or coryza) .....

(b) Cough ... ...

(c) Paroxysmal cough ... ...

(d) Whooping ... ...

(e) Vomiting ... ...

(f) Convulsions ... ...

2. Duration of COUGH (in days) prior to admission ..... days.

III

Relevant Clinical Findings on Admission:

Progress in Hospital: IV

1. Date Treatment Commenced.....

2. Where Nursed (encircle appropriately) Cell | Ward with less than 6 beds | Ward with more than 6 beds

DAY OF OBSERVATION.	TOTAL AMOUNT OF DRUG (in grams).	NUMBER OF PAROXYSMS. NOTED BY		SISTER'S ESTIMATE OF SEVERITY OF PAROXYSMS (mild, moderate or severe).	NUMBER OF VOMITS. NOTED BY	
		DAY STAFF.	NIGHT STAFF.		DAY STAFF.	NIGHT STAFF.
1st*						
2nd						
3rd						
4th						
5th						
6th						
7th						
8th						
9th						
10th						
11th						
12th						
13th						
14th						
15th						
16th						
17th						
18th						
19th						
20th						
21st						

* i.e., up to midnight on day of admission.

COMPLICATIONS: Date of onset ..... Date patient transferred to complications group† .....

Nature of Complication(s): V

†In patients who develop *any infection requiring treatment with sulphonamides or antibiotics other than those used in the trials* the treatment with the trial drugs should be stopped and the physician should treat the case as he thinks best. This record card should still be used for noting details of treatment, and progress and end result of the case.

NOTES BY PHYSICIAN. VI

DATE.	COMMENTS.

CLINICAL SUMMARY OF SEVERITY (to be completed on discharge): VII

OBSERVED TOXIC EFFECTS. VIII

DATE.	SYMPTOMS.

Special Examinations: IX

A. X-RAY EXAMINATIONS†:

DATE.	POSITION.	RESULT.

†Where possible, cases should be X-rayed on admission and thereafter weekly. Films other than in the A-P. position should only be taken where a lesion is suspected.

B. LABORATORY EXAMINATIONS*:

DATE.	NATURE OF SPECIMEN.	LABORATORY NUMBER.	RESULT.

*Wherever possible (*a*) Swabs, etc., should be taken on admission (1st day) and on the 2nd, 3rd, 8th and 11th days. All possible methods of bacteriological diagnosis should be used.

(*b*) Blood counts should be done on admission and subsequently weekly (or, during treatment, more frequently).

(*c*) Complement fixation tests may be necessary for retrospective diagnosis.

(c) Relevant Clinical Findings on Admission. Following admission to the ward a clinical examination was performed. The relevant findings were entered in this section and an attempt was made to assess the severity of the illness.

(d) Ward Sister's Observations: The ward sister made daily entries showing the amount of drug administered, the number of paroxysms and vomits in the day, and her estimate as to whether the paroxysms were on the whole mild, moderate or severe.

(e) Complications. Should any complication occur, the nature and date of onset was noted. For the purpose of the investigation, a complication was defined as any infective condition associated with whooping cough which the physician in charge considered to be severe enough to require immediate treatment by sulphonamides or another antibiotic. If a complication arose during the seven-day treatment period, administration of the trial drug was stopped and the fact recorded.

(f) Personal Observations. I made notes in the case records on the results of clinical examinations which were carried out daily. With the assistance of the ward sister an attempt was made to assess whether or not the course of the illness had been altered by the treatment.

(g) Clinical Summary of Severity. On discharge a brief clinical summary was made.

(h) Observed Toxic Effects. Any toxic effects of the drug were noted.

(i) X-ray Examinations. Radiological examination of the chest was carried out soon after admission and weekly thereafter. Films were taken routinely in the antero-posterior position, but, when necessary, other views were taken in order to define a suspected lesion.

(j) Laboratory Examinations. Routine bacteriological and haematological examinations were carried out. Shortly after admission I took the first per-nasal swab which was used to inoculate a Petri plate containing Bordet-Gengou medium. Thereafter swabs were taken on the second, third, eighth and eleventh days. By so doing it was possible to isolate the causal organism in many cases. Total differential leucocyte counts were made soon after admission and at weekly intervals thereafter. In order to maintain uniformity, I personally carried out these examinations. Capillary blood was obtained either from the nail bed in older children or from the heel in infants, and the standard methods employed were these described by Whitby and Britton (1950).

Duration of the Trial. At Ruchill Hospital the clinical trial commenced in December, 1950, and continued until May, 1951. During that six-month period all cases admitted were entered in the treatment register and were admitted to the trial if the necessary criteria were fulfilled.

Additional Investigations.

In addition to the antibiotic trial outlined above, it was decided to carry out simultaneously the following investigations:-

(a) Bacteriological Investigations. Stimulated and guided by Dr. Anderson's interest and experience in bacteriology, I decided to carry out personally all investigations for the isolation of the causal organism of whooping cough.

(b) Examination of Contacts. It was also decided to examine contacts of cases of whooping cough in order to determine if the Haemophilus pertussis was present in the nasopharynx in healthy persons and if a 'carrier state' existed.

(c) Radiological Examinations. Full radiological examinations of the chest were made in order to confirm the work previously carried out in Ruchill

Hospital by Lees (1950).

(d) Clinical Observations. Additional clinical notes were made in all cases to determine the effect of the drugs on clinical manifestations of the disease.

Methods employed at Ruchill Hospital.

Description of the Wards. At Ruchill Hospital, during the 1950-51 epidemic, two wards were devoted exclusively to the treatment of whooping cough. The wards 2 and 27 were identical in every respect, each having one compartment with six cots and one compartment with fourteen cots, separated by centrally placed duty room, kitchen and annexe. Each ward was staffed by an experienced sister, a staff nurse, nurses and domestics, and all were fully instructed on the special nursing problems associated with whooping cough.

Procedure on Admission. At Ruchill Hospital all whooping cough patients brought by ambulance were examined by the medical officer on duty prior to being admitted to the ward. A careful history of contact with another infectious disease was obtained by the ambulance nurse when she visited the patient's home, and the medical officer was able to take this into consideration when he examined the case. This procedure helped to minimise the risk of cross-infection and faulty diagnosis.

Shortly after admission, I visited the ward and made full clinical examination of the patient and assessed the suitability or otherwise for the trial. At this time a pernasal swab was taken and frequently a paroxysmal cough resulted. If the diagnosis was reasonably certain and the case considered suitable, the name was entered in the treatment register and treatment commenced.

Administration of the Drugs. In order to encourage close liaison between

the two wards the drugs were stored in ward 27 and the treatment register was kept in ward 2. The staff nurse in each ward was responsible for the drugs and their administration.

It was found by experience that the most convenient times for administering doses were 9.00 a.m. and 9.00 p.m.,as these two times followed the changing of napkins, etc., and did not interfere with feeding. The morning dose was given by the staff nurse and the evening dose by the night nurse. Little difficulty was experienced in the administration of the drugs. With children under nine months of age the drug was dissolved in a little water and given from a spoon. Older children could usually be persuaded to swallow the drug which was,if necessary, concealed in jam or some other pleasant-tasting substance. Administration of drugs to the middle group, of approximate age one to three years, presented difficulty on occasions, and sweetened condensed milk was discovered to be a suitable agent for disguising the bitter taste. In no instance was it found necessary to discontinue treatment because of difficulty in administration of the drug. On the other hand, the vomiting which frequently followed paroxysmal coughing proved troublesome in certain cases. If the child vomited within one hour of administration of the drug, the dose was repeated, but if vomiting occurred after the second dose, a note of this fact was entered in the case record card under 'Toxic Effects".

Recording of Paroxysms, Whoops and Vomits. A specimen is shown in Figure 5 of charts provided for this purpose, one of which was placed beside each cot. There was a space for each day in the week and separate columns for the use of day and night staffs. To simplify recording, all charts were renewed on the same day each week, with the effect that all were at the same stage at any one time. It was impossible to provide a nurse solely for the recording of paroxysms, but an

Figure 5.

RECORD OF PAROXYSMS, WHOOPS AND VOMITS.

Number ..... Name ..... Age ..... Sex .... Sheet .....

		DAY 8.30 a.m. - 8.30 p.m.		NIGHT 8.30 p.m. - 8.30 a.m.		TOTAL	WEIGHT
MONDAY	Spasms						
	Whoops						
	Vomits						
TUESDAY	Spasms						
	Whoops						
	Vomits						
WEDNESDAY	Spasms						
	Whoops						
	Vomits						
THURSDAY	Spasms						
	Whoops						
	Vomits						
FRIDAY	Spasms						
	Whoops						
	Vomits						
SATURDAY	Spasms						
	Whoops						
	Vomits						
SUNDAY	Spasms						
	Whoops						
	Vomits						

additional number was provided and as far as possible the nurses were specially selected. When it occurred, each paroxysmal cough was recorded on the appropriate chart, and it was noted whether or not the child whooped or vomited. The number of times the child whooped in each paroxysm was noted as accurately as possible.

Under test, many difficulties were apparent in this method of recording paroxysms. At night it occasionally happened that several children began to cough at the same time with the result that there were insufficient nurses in the ward to cope with all the children. Also it was often noted that babies could not be heard when older children were coughing. These difficulties were fully realised by the organisers of the trial, but they were minimised by the conscientious way in which the nurses carried out their duties.

Estimation of the Severity of the Paroxysms. These estimations were made by the ward sister who observed the child. For 21 days, daily estimations as to the severity of the paroxysms were made, using the following criteria for assessment:-

(a) Severe. A paroxysm was defined as severe when it was prolonged to such an extent that it caused the child to be exhausted, or if cyanosis were present, or if there was considerable expectoration, and when considerable nursing attention was required.

(b) Mild. When the child was not distressed, no expectoration was obvious, vomiting was not present, and no nursing attention was required during the paroxysm, it was considered to be mild.

(c) Moderate. All paroxysms which did not fit into the above two categories.

Estimation of Progress. Estimation of progress of each case was made by the ward sister and myself, assisted when necessary by the observations of the

staff nurses. On the eighth day of observation an attempt was made to assess clinically whether or not improvement had taken place during the treatment period. Improvement was recorded as being slight, good, or dramatic.

Methods of Bacteriological Examination.

In attempting to isolate the causal organism of whooping cough, the method found most successful at Ruchill Hospital had been the pernasal swab and this was the method used.

The Pernasal Swab. As described by Cockburn and Holt (1948), the pernasal swab was made from seven inches of a very fine flexible nickle chrome wire. A loop was formed from one end and the last quarter of an inch of the terminal end was bent back to hold a very thin pledget of cotton wool which was firmly wound round. The swab was placed in a six-inch by half-inch test tube which was plugged with cotton wool and the whole autoclaved.

Following use, the cotton wool was burned off and the wire straightened, after which the swab could be remade.

Prior to taking the swab the child was placed on his or her back and held securely by an assistant. The pernasal swab was then passed gently and swiftly backwards along the floor of the nose through both nostrils in turn until it touched the posterior wall of the nasopharynx. When the swab was fully inserted a half turn was made prior to withdrawal and replacement in the test tube. On occasions it was not possible to insert the swab into both nostrils, but in no case was the abnormality so great as to prevent effective swabbing. The procedure was easily carried out provided that the child was securely held and it caused little general disturbance. Frequently a paroxysm followed immediately after the swab had been taken, and therefore many new admissions were diagnosed clinically.

Bordet-Gengou Medium. In order to obtain uniformity, Bordet-Gengou agar base dehydrated by "Difco Laboratories" was used. When required the medium was rehydrated by suspending 4 grams of the base in 100 millilitres of 1 per cent solution of glycerol in distilled water. In order to dissolve the medium completely, the suspension was heated to boiling point and then sterilised in the autoclave for 15 minutes at 15 pounds pressuee (121°C.). After cooling to 45°C. to 50°C., sterile defibrinated horse blood was added to make a final concentration of 15 per cent, and 0.2 units per millilitre of penicillin was added. After thorough mixing it was poured into sterile Petri plates and care was taken that the surface was free from pitting. During cooling, the plates were only partially dried in order that there would remain in the medium sufficient moisture to withstand the prolonged incubation required for the growth of colonies of Haemophilus pertussis. The plates were then stored in a cool place until required. Fresh medium was prepared daily and frequently large quantities were required.

Inoculation of the Medium. The plate was inoculated as soon as possible after taking the pernasal swab. In the case of in-patients this was done immediately, but when contacts had been swabbed at home there was frequently up to three hours' delay. The swab was removed from the test-tube in the laboratory and stroked over half the plate and then lightly stroked eight times over the remaining half of the plate. A separate plate was used for each swab.

The inoculated plate was then placed in a tin and incubated at 37°C. for up to six days. It was my custom to use separate tins each day as this simplified examination. Clean and sterilised National Dried Milk tins were found to be convenient for the purpose.

Identification of Haemophilus Pertussis. I examined the plates daily

but did not open them until incubation had been carried out for 72 hours. A hand-lens was used and the entire surface of the medium carefully examined. Haemophilus pertussis appeared as tiny mercury-drop-like colonies, of which in a sparsely inoculated plate there were sometimes only one or two. On occasions I have discovered the entire plate covered by very small colonies giving the classical appearance of aluminium paint. Plates with no growth were replaced in the tin and incubation continued with daily examinations for six days. Contaminated plates often had to be discarded but on occasion it was possible to cut out the affected portion of medium. When secondary invaders were present, the type of organism and the extent of contamination were noted.

Suspicious colonies were removed from the plate by straight platinum wire and identified morphologically and by slide agglutination. The organism was first stained by Gram's method when it appeared as a small gram-negative coccobacillus, somewhat resembling Haemophilus influenzae. It was noted, however, that the colonies of Haemophilus influenzae were flatter and not so easily removed as was the case with Haemophilus pertussis. Slide agglutination tests were then carried out. A uniform suspension of a suspected colony in normal saline was prepared and divided into three portions on a grease-free slide. To one of the drops of the suspension there was added a loopful of specific rabbit antisera to Haemophilus pertussis, and a loopful of the specific rabbit antisera to Haemophilus parapertussis was added to the second drop of suspension. The third drop of suspension acted as a control. After rocking the slide for 30 seconds, agglutination of the organism became obvious microscopically in positive cases, there being no similar agglutination in the parapertussis or control suspensions.

Examination of Contacts. As many features of the disease are still

undetermined, it was decided to observe as many contacts as possible, and it was hoped that some additional information might be gained. During epidemics of scarlet fever and cerebro-spinal fever, it is frequently possible to isolate the causal organism from the throat and nasopharynx of normal healthy carriers as well as from clinical cases of the disease. With a view to ascertaining whether or not a similar carrier state existed in whooping cough, three groups of contacts were observed. A copy of the form used for recording the list of contacts of each case and the results of pernasal swabs is shown in Figure 6.

(a) Nursing and Domestic Staff. In the two whooping cough wards at Ruchill Hospital, the nursing and domestic staff were examined and serial pernasal swabs taken at fourteen days intervals. In addition, pernasal swabs were taken from the staff of a residential nursery where there had been several whooping cough patients.

(b) Family Contacts. I visited the homes of several patients who lived near the hospital. Information was obtained regarding each member of the family as to whether or not he or she had previously had whooping cough or had been immunised against the disease. Pernasal swabs were taken from all of these contacts.

(c) Contacts in Institutions. I visited institutions, such as residential nurseries, and took pernasal swabs from all the child contacts. In each case, records were made as to previous history of having had whooping cough and to immunisation state. It was also noted if the contact had been close, e.g., if the child had slept in the same room as the patient.

Figure 6.

Whooping Cough Contacts.

Name of Patient ..... Ward .....

Address .....

Name	Age	Relationship to Patient	Date Swab taken	Result

Ruchill Hospital,
Glasgow.

Date .....

CHAPTER 5.

THE MEDICAL RESEARCH COUNCIL REPORT UPON THE CLINICAL TRIAL OF ANTIBIOTIC TREATMENT CONDUCTED IN EIGHT INFECTIOUS DISEASES HOSPITALS.

A report by the Whooping Cough Sub-Committee of the Antibiotics (Non Tuberculous Conditions) Committee of the Medical Research Council was published in the Lancet in June, 1953. The trial was carried out in eight infectious diseases hospitals during the years 1950-1951, employing methods previously described in Chapter 4.

Three hundred and seventeen patients were treated at the various centres, but 23 of these were later excluded because all the necessary criteria had not been fulfilled. Ruchill Hospital supplied the largest individual total number of patients, and 94 were included in the final analysis: 31 were in the chloramphenicol group, 31 in the aureomycin group, and 32 in the control group. It should be noted that these figures do not exactly correspond with the separate analysis which I carried out. This was due to minor differences in interpretation of the criteria for inclusion. For example, one of the Ruchill patients who was found to be infected by Haemophilus parapertussis was excluded from the final analysis by the committee but has been included in my own series.

The Medical Research Council analysed the records of 294 patients, of which 98 were in the chloramphenicol group, 96 in the aureomycin group and 100 in the control group. There was remarkable uniformity at each hospital in the distribution of patients in the three treatment groups according to age and sex. This emphasised the excellence of the treatment registers which had been compiled for the purpose. Of the children treated in the investigation, 54.8 per cent were females but no separate analysis by sex was made.

Although diagnosis was based chiefly on clinical grounds, Haemophilus pertussis was isolated from 47 per cent. of the patients.

The original intention was to observe each child for 20 days, but this

was not always practicable, and some children were discharged before the observation period was completed. However, allowance has been made for this in the final analysis

Each patient was placed in one of three groups according to duration of symptoms prior to the commencement of treatment. Eighty-five children who had symptoms of 1 to 8 days' duration before commencement of treatment were classified as "early", 147 children who had symptoms 9-15 days before commencement of treatment were classified as "intermediate", and 67 children who had symptoms 16-20 days before commencement of treatment were classified as "late". The date of onset of illness was taken as being the day on which the first sign was noted and not the day of onset of the paroxysmal cough. No patient who had been ill for longer than 21 days was admitted for investigation.

The results of the three treatment groups were assessed by analysing (a) the number of paroxysms per case per day, (b) the severity of the paroxysms, (c) the number of complications, (d) the number of deaths, and (e) the bacteriological findings at intervals during the observation period.

Number of Paroxysms.

For each treatment group the average number of paroxysms per case per day was calculated separately. The results were recorded on three graphs, one for early cases, one for intermediate cases, and one for late cases. The analysis showed that early cases who had received antibiotic treatment, fared better when compared with the controls than did those treated when the illness had lasted longer than eight days. There appeared to be little difference between the two antibiotics, aureomycin and chloramphenicol, and further analysis, therefore, was made only between treated and control patients.

The average number of paroxysms per case in the treated group was less than in the control group for the early, intermediate and late cases, and the differences were consistent throughout the period of observation. In the early cases the difference between treated and control groups was greatest. This was shown both by calculating the average number of paroxysms per case, and by calculating the percentages of cases showing 0-9, 10-19, and 20 or more paroxysms in various days. The differences were statistically significant in both cases.

Severity of Paroxysms.

In each case the estimation of severity of the paroxysms was made daily by the ward sister and the percentages of patients in which paroxysms were mild, moderate and severe were tabulated in five four-day periods. The greatest effect on the severity of the paroxysms was again seen in the early cases where there was a statistically significant difference between patients in the treated and control groups. In the intermediate cases, while the effect on severity was not so marked, the difference in the number of severe paroxysms between treated and untreated cases was nevertheless statistically significant.

The analysis indicated that treatment had had a greater effect on the severity than the total number of paroxysms.

Complications and Deaths.

During the observation period, 19 patients, seven in the control group, seven in the aureomycin group, and five in the chloramphenicol group, developed respiratory complications. In five cases (three in the control group and two in the chloramphenicol group), the complications arose during the period when the drug was being administered. In all other cases, the complications arose after cessation of treatment.

In addition there were three fatal cases, one in each treatment group. The patient in the control group was a male child aged six weeks, who developed bronchopneumonia on the 5th day of observation and died on the 10th day despite the administration of penicillin and sulphonamides. This child was very young and the fatal outcome is not surprising. The other two deaths which occurred in the Ruchill series will be discussed later.

It is interesting to note that none of the complicated and fatal cases occurred in patients treated within eight days of the onset of symptoms.

Bacteriological Results.

Patients admitted to the trial were swabbed on the 1st, 2nd, 3rd, 8th and 11th days. The general conclusion reached was that on the 8th and 11th days the percentage of positive cases was less in the treated than in the control groups for early, intermediate and late cases.

Toxic Effects.

Presumed toxic effects were made in 28 patients, of whom 12 were in the chloramphenicol group, 15 in the aureomycin group, and one in the control group. In 19 patients, vomiting appeared to be due to administration of the drug, and in a further five there was anorexia. Diarrhoea was noted in two patients in the chloramphenicol group, and redness of the buttocks in one case in the aureomycin group. One patient in the aureomycin group developed an urticarial rash as the result of treatment.

It is worth noting that four children, three in the aureomycin group and one in the chloramphenicol group, had to be excluded from the final analysis because of repeated vomiting of the drug.

Discussion.

The main conclusion reached in the study was that early recognition and early antibiotic therapy of whooping cough would help to reduce the severity of the infection, but that little was to be gained from the antibiotic treatment of cases in which even slight symptoms had been present for more than a week.

One of the great difficulties in assessing the effectiveness of a new treatment is to obtain a sufficient number of cases. In the recent trial of the antibiotics in whooping cough, the difficulty was overcome by making use of eight hospitals throughout the country. This method, although still uncommon, is becoming more recognised as a means of accumulating a sufficient number of cases to carry out a strictly controlled trial. As one of the purposes of the trial was to obtain information as quickly as possible, it is most unfortunate that two years elapsed between the completion of the clinical trial and the publication of the report.

C H A P T E R 6.

DESCRIPTION OF THE PATIENTS ADMITTED TO THE CLINICAL TRIAL IN RUCHILL HOSPITAL.

History obtained from the Parents and Guardians.

Social Class and Housing Conditions. As it was considered that the social class and housing conditions might well have an important bearing on the progress of the disease, careful note was kept as to these factors. Of the 96 patients considered in the final analysis, 69.6 per cent came from the social class IV and V. There were 19 children from institutions, two from general children's hospitals, and 17 from residential homes in the city. These patients are shown separately and are not analysed by social class, as is shown in Table 5.

Table 5.

Social Class of the 96 Patients admitted to the Clinical Trial.

Social Class	Number	Per Cent
I	0	-
II	0	-
III	10	10.6
IV	37	38.4
V	30	31.2
Institutional	19	19.8
Total	96	100

There were 67.5 per cent of patients who came from overcrowded houses and 62.4 per cent lived in one- or two-apartment houses, as shown in Table 6. This finding is typical among patients in Glasgow fever hospitals.

Table 6.

Housing Conditions from which Patients were admitted.

Number of Apartments	Patients		Overcrowded	
	Number	Per Cent	Number	Per Cent
One	32	33.3	31	32.3
Two	28	29.1	22	23.2
Three	12	12.5	2	2.0
Four	5	5.3	0	-
Institutional	19	19.8	0	-
Total	96	100	65	67.5

Immunization State. Only nine (9.4%) patients had received immunization against whooping cough and all these came from institutions. It was noted, incidentally, that 55 (57%) of the 96 patients had neither been immunized against diphtheria nor vaccinated against smallpox.

Previous Illness. It was considered that previous illness and especially diseases of the chest might influence the course of whooping cough, and the findings are recorded in Table 7.

Table 7.

Previous Illness in 96 Whooping Cough Patients, divided according to Treatment Groups.

Illness	Control Group	Aureomycin Group	Chloramphenicol Group	Total
Another Infectious Disease	5	6	13	24
Gastroenteritis	3	1	5	9
Chest Disease (Non-Specific)	4	3	4	11
Other	3	3	3	9
No Illness	19	23	17	59

There was no history of previous illness in 59 of the patients. Twenty-four patients had had another infectious disease and, in addition, nine had suffered from gastro-enteritis. A previous history of chest disease, mainly bronchitis and bronchopneumonia, was recorded in 11 patients, three of whom were in the aureomycin group, four in the chloramphenicol group, and four in the control group.

History of the Onset of the Illness. Parents and guardians were carefully questioned as to the date of onset of the illness and to the nature of the first sign noted. The date of the onset was taken as being the day on which the child sickened and not the day of onset of the paroxysmal cough. Great difficulty was experienced in obtaining accurate information, and this appeared to have no relationship to the intelligence of the parents. The same difficulty was noted when obtaining information from trained nurses in hospitals and children's homes. Frequently it was noted that apparently less intelligent mothers were most observant, and they could often associate the child's illness with some other event. For example, it was common for a mother to say that the child became ill 'four days after the New Year' or 'the same day that Mrs. Smith died'. When such a statement was made it was often possible to fix the date with great accuracy.

In some cases, general malaise, anorexia, or signs of respiratory catarrh prior to the onset of cough were reported by the mothers. In a further group a dry cough was the first sign, and in a few cases the paroxysmal cough was the first sign noted. The dates of onset of signs prior to cough, dry cough, and paroxysmal cough were noted as accurately as possible. In 36 (37.5%) patients, a history of general malaise, etc., was noted prior to the onset of cough. In 45 (46.9%)

patients, the first sign was a dry cough, and in remaining 15 (15.6%) patients there was apparently no catarrhal stage at all, as is shown in Table 8.

Table 8.

The First Sign of Illness noted by Parents or Guardians in 96 Whooping Cough Patients.

First Sign	Number of Patients	Per cent
General Malaise, Anorexia, Coryza, etc.	36	37.5
Dry Cough	45	46.9
Paroxysmal Cough	15	15.6
Total	96	100

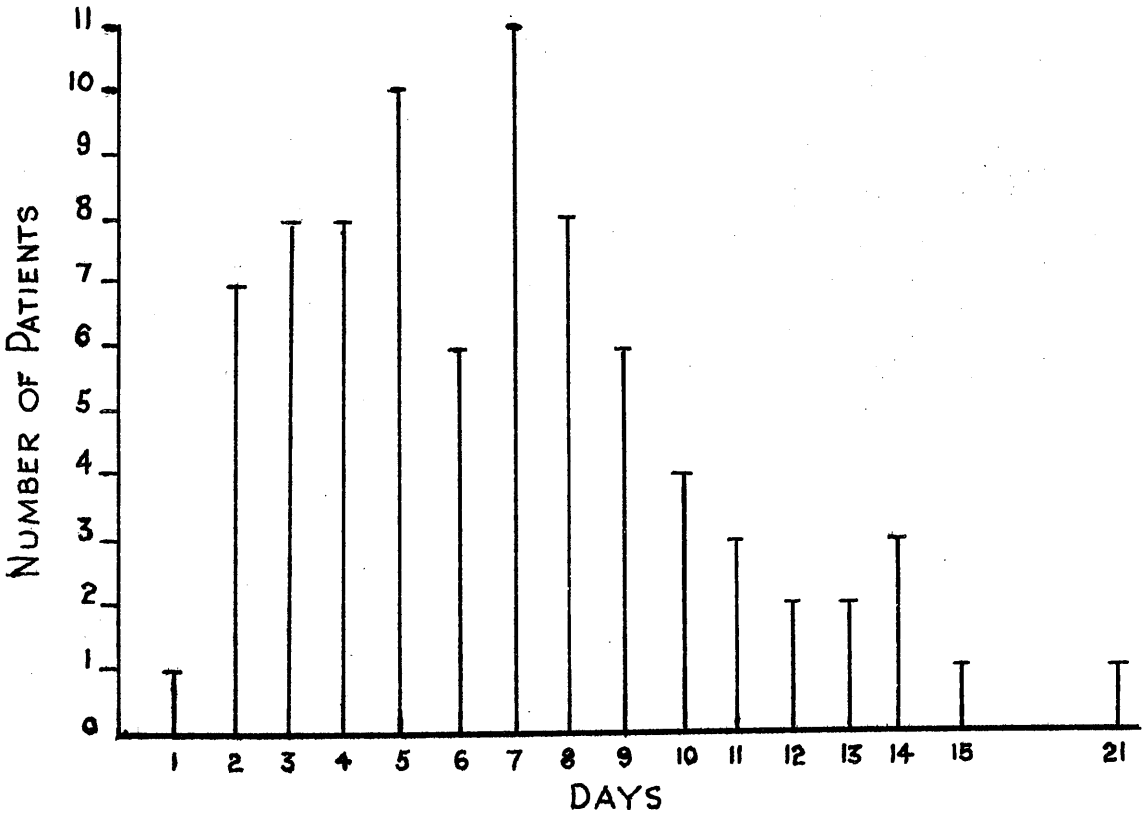
Duration of the Catarrhal Stage. In the 36 patients who had signs of illness prior to the onset of cough, the average duration of this period was 5.3 days, there being extremes of one and 13 days, and the mode was five days. In 18 of these patients, the first cough noted was paroxysmal, but in the remaining 18, there was a varying interval between the onset of the cough and its becoming paroxysmal. This interval varied from 2 to 15 days, with an average of 5.1 days and a mode of six days.

In 81 of the 96 patients there was a catarrhal stage, and the interval, in days, between the onset of illness and the establishment of the paroxysmal stage is shown in Figure 7. The average duration of the catarrhal stage was 6.7 days, and it was as short as one day and as long as 21 days, with a mode of seven days.

Institutional Cases. In view of these conflicting findings, and obvious difficulty in obtaining an accurate history, it was decided to pay special

FIGURE 7.

THE DURATION [In Days] OF THE CATARRHAL STAGE IN 81 WHOOPING COUGH PATIENTS



attention to the histories of the 19 institutional cases. It seemed likely that earlier symptoms, such as malaise, anorexia, etc., might have been noticed in institutions. Upper respiratory signs prior to the onset of a dry cough was noted in five patients, and a dry cough was the first sign noted in 8 of the 19 patients. In the remaining six patients, the first sign noted was the paroxysmal cough. It would appear, therefore, that in 13 (68.4%) of the 19 patients, there was a detectable catarrhal stage, and that in 6 (31.6%) patients, the catarrhal stage was absent.

In five patients there were upper respiratory symptoms prior to the onset of cough for an average period of 5.6 days with a mode of six days. In the 13 patients, in which there was a catarrhal stage prior to the onset of cough, it was reported that the first cough was paroxysmal. The duration of the catarrhal stage in 13 institutional cases varied from 2 to 21 days, with an average of seven days and a mode of seven days.

Whooping. Fifty-six (58.1%) of the 96 patients were said to have whooped prior to admission. Little reliance can be placed on this figure as many of the parents seemed unable to recognize a whoop.

Vomiting. It was reported that 47 (49%) of patients had vomited before admission. It was soon realised, however, that expectoration was often confused with vomiting, and so little reliance can be placed on this figure.

Convulsions. Four patients were said to have suffered from convulsions before admission. In three of these patients there was only one alleged convulsion in each case, but no reliable witness was present. The fourth child was a male child aged two years who was in the tenth day of illness when he had two short convulsions lasting about five minutes. The second of these was witnessed

by the general practitioner. The child had no convulsion after admission to hospital.

Confirmation of Diagnosis.

No patient was included in the final analysis unless either bacteriological confirmation had been attained or at least two of the following primary criteria were satisfied:-

(a) Whoop heard by the ward sister or myself.

(b) History of contact with a known case of whooping cough.

(c) Raised leucocyte count with a definite lymphocytosis.

Bacteriological confirmation also obtained in 50 (52.1%) of the patients. Haemophilus pertussis was isolated from 49 cases, and Haemophilus parapertussis was isolated from one case. Of the 45 patients who had negative bacteriological tests, the three criteria were satisfied in 15 patients. Whoop was heard and the haematological findings were significant in 10 patients. There was a contact history and significant haematological findings in six patients.

Age and Sex of Groups.

Patients were divided by the treatment register into six groups according to age and sex, and further subdivided according to the treatment given. Thirty-three patients received aureomycin, 32 received chloramphenicol, and 31 acted as controls, as is shown in Table 9.

Exactly the same number of males as females were treated in the series. In the aureomycin group 17 (51.5%) patients were female, and in the chloramphenicol group 17 (53.1%) patients were female, and in the control group 14 (45.2%) patients were female. Generally speaking, the groups appeared comparable with regard to sex ratio, but there was a slight preponderance in the number of males in the 0-1

Table 9.

Number of Patients Treated, Divided by Age, Sex and Type of Treatment.

Age (in years)	Control			Aureomycin			Chloramphenicol		
	M	F	T	M	F	T	M	F	T
0-1	9	6	15	8	8	16	9	6	15
1-3	5	5	10	6	5	11	5	5	10
3-5	3	3	6	2	4	6	1	6	7
All Ages	17	14	31	16	17	33	15	17	32

M = Male; F = Female; T = Total.

year age-group. When divided into age and sex groups, the numbers appeared to be too small to allow any conclusions to be drawn. It did not appear from preliminary inspection that sex played any part in the course of the illness, and no separate analysis by sex was made.

In the 0-1 year age group, 16 patients were treated with aureomycin, 13 with chloramphenicol, and 15 acted as controls. In the 1-3 year age-group, 11 were treated with aureomycin, 10 with chloramphenicol, and there were 10 controls. In the 3-5 year age-group, six were treated with aureomycin, seven with chloramphenicol, and six acted as controls. All three treatment groups are, therefore, comparable as regards age distribution.

Duration of Illness prior to Admission to Hospital.

In all cases, treatment was started within 24 hours of admission to hospital. As the course of the illness lasts for at least six weeks, it is of vital importance that the duration of illness prior to the commencement of treatment be taken into account. Patients were, therefore, divided into three groups.

(a) Early cases were defined as these with symptoms for 1-8 days before treatment was commenced.

(b) Intermediate cases were defined as these with symptoms for 9-15 days before treatment was commenced.

(c) Late cases were defined as these with symptoms for 16-21 days before treatment was commenced.

There were 27 patients in the early group, nine treated by aureomycin, nine by chloramphenicol, and nine acted as controls, as shown in Table 10. Forty-seven patients were placed in the intermediate group, and of these 16 were treated by aureomycin, 17 by chloramphenicol, and 14 acted as controls. There

Table 10.

Day of Illness of Patients on Admission, Divided by Age and Treatment Groups.

Duration of Illness Prior to Admission	Control Group				Aureomycin Group				Chloramphenicol Group				All Groups			
	0-1 Year	1-3 Years	3-5 Years	All Ages	0-1 Year	1-3 Years	3-5 Years	All Ages	0-1 Year	1-3 Years	3-5 Years	All Ages	0-1 Year	1-3 Years	3-5 Years	All Ages
Early Cases (1-8 Days)	6	2	1	9	5	3	1	9	6	3	0	9	17	8	2	27
Intermediate Cases (9-15 days)	5	6	3	14	9	4	3	16	6	6	5	17	20	16	11	47
Late Cases (16-21 Days)	4	2	2	8	2	4	2	8	3	1	2	6	9	7	6	22
Total	15	10	6	31	16	11	6	33	15	10	7	32	46	31	19	96

were 22 patients in the late group, eight on aureomycin, six on chloramphenicol, and eight controls.

Of the 27 early cases, 17 (62.9%) were in the 0-1 year age-group. This high percentage was due to outbreaks of whooping cough in residential homes for infants.

When the patients in the three age-groups were divided separately according to whether they were early, intermediate, or late, the numbers were generally comparable. For example, in early cases aged 0-1 year, there were five patients on aureomycin, six on chloramphenicol, and six controls. In intermediate cases aged 1-3 years, there were four on aureomycin, six on chloramphenicol and six controls. In late cases aged 3-5 years, there were two on aureomycin, two on chloramphenicol, and two controls.

Severity of the Illness.

Soon after admission, in each case an estimate was made as to whether the illness was mild, moderate or severe. Cases were judged as being mild in 11 (33%) of the aureomycin patients, 8 (25%) of the chloramphenicol patients, and 10 (32%) of the controls, as is shown in Table 11. Cases were judged as being moderate in 14 (43%) of the aureomycin patients, 16 (50%) of the chloramphenicol patients, and 13 (42%) of the controls. Cases were judged as being severe in 8 (24%) of the aureomycin patients, 8 (25%) of the chloramphenicol patients, and 8 (25%) of the control. There was a comparable distribution of mild, moderate and severe cases in each treatment group.

An attempt was made to compare the severity of illness with the duration of illness before admission to hospital, and the findings are shown in Table 12. No positive correlation was obtained.

Table 11.

Severity of Illness of Patients, Divided by Age and Treatment Groups.

Severity	Age Group 0-1 Year				Age Group 1-3 Years				Age Group 3-5 Years				All Ages			
	C.	A.	Ch.	T.	C.	A.	Ch.	T.	C.	A.	Ch.	T.	C.	A.	Ch.	T.
Mild	6	5	3	14	3	5	2	10	1	1	3	5	10	11	8	29
Moderate	5	8	9	22	5	3	5	13	3	3	2	8	13	14	16	43
Severe	4	3	3	10	2	3	3	8	2	2	2	6	8	8	8	24
All Patients	15	16	15	46	10	11	10	31	6	6	7	19	31	33	32	96

C. = Control Group
A. = Aureomycin Group
Ch. = Chloramphenicol Group
T. = Total

Table 12.

Severity of Illness of Patients,
Divided by Treatment Groups and Duration of Illness on Admission.

Severity	Early (1 to 8 days)				Intermediate (9 to 15 days)				Late (16 to 21 days)				All Patients			
	C.	A.	Ch.	T.	C.	A.	Ch.	T.	C.	A.	Ch.	T.	C.	A.	Ch.	T.
Mild	2	3	3	8	4	5	4	13	4	3	1	8	10	11	8	29
Moderate	1	4	5	10	9	8	7	24	3	2	4	9	13	14	16	43
Severe	6	2	1	9	1	3	6	10	1	3	1	5	8	8	8	24
Total	9	9	9	27	14	16	17	47	8	8	6	22	31	33	32	96

C. = Control Group
A. = Aureomycin Group
Ch. = Chloramphenicol Group
T. = Total

Equality of the Groups.

In a strictly controlled clinical trial, it is essential that the patients who have been treated are comparable with these who have not been treated. I have considered from various aspects the numbers of patients in each of the three treatment groups, and the reasons for claiming that the treatment groups are comparable are summarized below.

Factors concerning Patients	Aureomycin Group	Chloram-phenicol Group	Control Group
Total Numbers	33	32	31
Sex - Male	16	15	17
Female	17	17	14
Age- Groups - 0-1 year	16	15	15
1-3 years	11	10	10
3-5 years	6	7	6
Duration of Illness prior to Commencement of Treatment:			
Early (1-8 days)	9	9	9
Intermediate (9-15 days)	16	17	14
Late (16-21 days)	8	6	8
Severity of Illness:			
Mild	11	8	10
Moderate	14	16	13
Severe	8	8	8

Admission Register.

During the six-month period from 16th December, 1950, until June, 1951, 194 patients were admitted with the diagnosis of 'whooping cough' to wards 2 and 24 at Ruchill Hospital. During that period a further 21 whooping cough patients were admitted to other wards in the hospitsl, making a total of 215 patients. Of the 215 patients, only 101 fulfilled the criteria laid down for admission to the trial:

and of the 101, five had to be excluded at a later date. In four of the excluded patients, the accuracy of the history obtained was doubtful, and it was considered possible that the children had been ill for longer than 21 days. The other child who was excluded was discovered radiologically to have a pleural effusion. Of the remaining 114 patients not admitted to the trial, 37 were not suffering from whooping cough.

The reasons for exclusion of 77 whooping cough patients from the trial are detailed in Table 13.

Table 13.

Reason for Exclusion of 77 Whooping Cough Patients from the Antibiotic Trial.

Late cases	28
Concurrent Bronchopneumonia ..	23
Concurrent with another Infectious Disease	2
Over five years of age	5
Treated with Aureomycin and Chloramphenicol before Admission	5
Critically ill	11
Other conditions	3
Total	77

There were 28 late cases, that is, patients who had been ill for longer than 21 days before admission to hospital. These patients were admitted mainly because of persistent chest complications. Urgent treatment was required in 23 patients who were suffering from bronchopneumonia. Two patients were suffering from another infectious disease as well as whooping cough, and five were unsuitable because they had been given one of the trial drugs prior to admission. Eleven patients, who appeared to be critically ill, were not admitted to the

trial, eight of these 11 patients died, one had convulsions on admission but made a good recovery, one had primary tuberculosis and after prolonged sanatorium treatment made a satisfactory recovery, and one was cachectic and in a grossly neglected state. Three other whooping cough patients were admitted, and of these, one had acute appendicitis, one had tuberculous meningitis, and one, who was suffering from a head injury, was in need of observation. Only five patients were over five years of age, and the oldest was an 18-year-old student nurse from a general hospital. The exclusion from the trial of patients over the age of five years, therefore, seems to have been justified

The Trial Patients.

Ninety-six uncomplicated whooping cough patients were admitted to the trial. It was attempted, first of all, to ascertain the reasons for having had the patients admitted to hospital. Seven categories were used, as is shown in Table 14, and it was discovered that only four patients did not fall into at least one of these.

Table 14

Possible Reason for Admission to Hospital of 96 Whooping Cough Patients.

Under one year of age	46
Patients severely ill	24
Institutional cases	19
Bad Home Conditions	64
Chest Complication suspected ...	33
Suspected Convulsions	4
Admitted as another Infectious Disease	4

By far the commonest single factor affecting Glasgow patients was the home conditions which were bad in 64 instances. Where overcrowded home conditions

existed there was ample justification for admission of the whooping cough patient. I also feel that it was justifiable to admit any whooping cough patient under the age of one year, and there were 46 of these. Twenty-four of the 96 patients were severely ill, and 19 more came from institutions. It is interesting to note that 33 of the 96 patients were admitted with the diagnosis 'whooping cough and pneumonia'. Many general practitioners appear to have difficulty in differentiating the signs of bronchitis, which are present in the early stages of the illness, from those of true bronchopneumonia. Four patients were suspected of having convulsions and a further four patients were admitted as another infectious disease.

When these seven criteria were considered in relation to each patient it was discovered that 25 patients satisfied one of the criteria. Forty-two patients satisfied two of the criteria, 23 patients satisfied three of the criteria, and two patients satisfied four of the criteria.

Summary.

A general description of the background of the patients admitted to the trial has been given, and the criteria laid down for acceptance are discussed.

A brief description of the whooping cough cases not admitted to the trial, with reasons for their exclusion, is given.

Reasons are given for considering the two groups as being comparable.

CHAPTER 7.

GENERAL AND CLINICAL OBSERVATIONS MADE UPON PATIENTS AND THEIR ILLNESSES DURING THE INVESTIGATION.

In addition to the notes made on the Medical Research Council record card, careful notes of the results of daily clinical examinations were made. The various clinical manifestations of the disease will now be discussed.

Temperature, Pulse and Respiration.

Of the 96 uncomplicated whooping cough patients admitted to the trial 71 (73.8%) of cases were apyrexial throughout their stay in hospital, as shown in Table 15.

Table 15.

Pyrexia noted in the 96 Whooping Cough Patients admitted to the Trial, divided according to Treatment Groups.

Treatment Group	Nil	Under 100°F.	100°-101°F.	Over 101°F.	Total
Control	25	2	4	0	31
Aureomycin	22	9	1	1	33
Chloramphenicol	24	5	0	3	32
All Patients	71	16	5	4	96

In 16 patients the temperature was intermittent during the first two to five days in hospital and did not exceed 100°F. Over and above this, in five patients the temperature exceeded 100°F., but was less than 101°F., but in all cases the temperature had returned to normal within three days. In the remaining four patients, temperatures over 101°F. were recorded, but in no case did it exceed 102.6°F. In three of these patients, this pyrexia only lasted for two days, and in one patient it was present for three days and returned to normal on the sixth day in hospital.

Pulse and respiration rates were not affected by the illness and were raised only in proportion to the temperature.

Coryza.

A catarrhal condition of the nasopharyngeal mucosa was present in 54 (56.3%) patients, 17 in the aureomycin group, 18 in the chloramphenicol group, and 19 in the control group, as is shown in Table 16.

Table 16.

Coryza noted in the 96 Whooping Cough Patients admitted to the Trial, divided according to Treatment Groups.

Treatment Group	Coryza Absent	Coryza Present	Total
Control	12	19	31
Aureomycin	16	17	33
Chloramphenicol	14	18	32
All Patients	42	54	96

The average duration of the coryza was 9.4 days in the 54 patients in which it was present. For the aureomycin group, the average duration was 10.2 days, for the chloramphenicol group 8.2 days, and for the control group 8.9 days. Reference to Table 17, which illustrates the frequency distribution, indicates that in the chloramphenicol group, coryza tended to clear up more quickly than in the control or aureomycin group.

Table 17.

Frequency Distribution of the Duration (in Days) of Coryza divided according to Treatment Groups

Treatment Group	Duration in Days																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Control	-	1	-	1	2	1	2	1	2	2	1	1	1	-	1	-	1	1	-	1	-	-
Aureomycin	-	-	-	2	1	1	3	1	-	1	1	1	-	1	1	-	-	-	-	1	1	1
Chloramphenicol	-	-	-	2	2	2	2	2	1	4	1	1	-	-	1	-	-	-	-	-	-	-
All Groups	-	1	-	5	5	4	7	4	3	7	3	3	1	1	3	-	1	1	-	2	1	1

Listlessness and Sleep.

Listlessness was clinically noticeable in 13 cases, being present in eight severe and five moderate cases. Two of these patients died, and in the remaining 11, the average duration of listlessness was six to eight days.

Two patients, both of whom were severely ill, were restless at night to such an extent that sleep was disturbed. Both these cases are included in the group that were listless during the day. All the remaining patients appeared to sleep well and had paroxysmal cough only when disturbed. I made frequent visits to the wards at night and was impressed by the fact that on the whole the patients' sleep did not appear to be unduly disturbed by paroxysmal coughing. This was probably the result of prompt and skilful handling by the nursing staff.

Gastro-intestinal Tract Disturbance.

Three manifestations of upset of the gastro-intestinal tract, namely, vomiting, anorexia and diarrhoea, were observed. These will now be discussed.

Vomits. Each time a patient vomited a note of the incident was recorded. Analysis showed that 17 of the 96 patients did not vomit at any time, and of these, six were in the aureomycin group, six were in the chloramphenicol group, and five were in the control group. Regular vomiting, that is, vomiting on at least one occasion in five out of any seven days of observation, occurred in 36 patients. Of these 36 patients, 16 were in the aureomycin group, 11 in the chloramphenicol group, and 9 in the control group. When the average number of times each child vomited was considered in 4-day periods, it was noted that during the treatment period it was 3.9 for the aureomycin treated patients, 3.5 for the chloramphenicol treated patients, and 2.4-2.2 for the control patients, as is shown in Table 18.

Table 18.

Average Number of Times Each Child Vomited (by 4-Day Periods), Divided according to Treatment Groups and Duration of Illness prior to Admission to Hospital.

Observation Period (Days)	Aureomycin Group				Control Group				Chloramphenicol Group			
	Early Cases	Inter-mediate Cases	Late Cases	All Cases	Early Cases	Inter-mediate Cases	Late Cases	All Cases	Early Cases	Inter-mediate Cases	Late Cases	All Cases
1-4	2.1	3.2	8.0	3.9	1.1	2.3	3.4	2.4	2.4	4.2	2.3	3.5
5-8	2.2	3.1	6.6	3.9	1.6	2.7	2.6	2.2	1.3	5.0	0.7	3.5
9-12	1.6	2.4	3.2	2.3	4.6	2.3	3.8	3.3	1.3	3.6	0.5	2.3
13-16	2.1	2.6	3.2	2.5	2.9	2.6	2.3	2.9	0.4	3.5	0.3	2.2
17-20	0.3	1.4	4.8	1.8	2.7	2.0	2.0	2.4	0.4	2.3	1.1	1.8
Number of Patients	9	16	8	33	9	14	8	31	9	17	6	32

During the 13-16 day period, the average number of vomits was 2.5 for the aureomycin group, 2.2 for the chloramphenicol group, and 2.9 for the controls. It would appear, therefore, that during the treatment period, patients who were receiving antibiotic therapy vomited more frequently than did the controls.

When the duration of illness prior to admission to hospital is considered it would appear that during the treatment period early cases vomited less frequently than did intermediate cases. For example, on days 5-8, in the chloramphenicol group, the average number of vomits was 1.3 for early cases and 5.0 for intermediate cases; in the aureomycin group, the average was 2.2 for early cases and 3.1 for intermediate cases; and in the control group, the average was 1.6 for early cases and 2.7 for late cases. Late cases in the aureomycin group vomited, on an average, 8.0-6.6 times during the first eight days of observation, while control patients vomited 3.4-2.6 times during the same period.

Generally speaking, it was found that the number of times each child vomited was greater in the age-group 3-5 years than in children under 3 years of age, as is shown in Table 19. This was especially so in the aureomycin group where, during the period 1-4 days, the average number of vomits was 8.3 for children aged 3-5 years, 3.8 for children aged 1-3 years, and 2.7 for children aged 0-1 year. Similar figures for the control patients was 4.7 for children aged 3-5 years, 1.2 for children aged 1-3 years, and 2.0 for children aged 0-1 year. This finding was not the same as for patients in the chloramphenicol group.

Loss of Appetite. Appetite tends to be poor throughout the disease. Special note was made of patients in whom it was exceptionally poor or absent.

Table 19.

Average Number of Times Each Patient Vomited (by 4-Day Periods), Divided according to Treatment and Age Groups.

Observation Period (Days)	Aureomycin Group				Control Group				Chloramphenicol Group			
	Age 0-1 Year	Age 1-3 Years	Age 3-5 Years	All Ages	Age 0-1 Year	Age 1-3 Years	Age 3-5 Years	All Ages	Age 0-1 Year	Age 1-3 Years	Age 3-5 Years	All Ages
1-4	2.7	3.8	8.3	3.9	2.0	1.2	4.7	2.4	4.2	3.3	2.2	3.5
5-8	1.7	5.1	7.8	3.9	2.1	3.1	4.7	2.2	3.7	3.5	3.7	3.5
9-12	1.3	1.8	5.8	2.3	2.5	3.4	5.3	3.3	2.0	3.2	2.2	2.3
13-16	2.0	1.8	5.5	2.5	2.5	2.2	5.2	2.9	3.6	1.5	0.1	2.2
17-20	1.6	1.7	2.8	1.8	2.4	1.4	4.5	2.4	2.6	0.6	2.2	1.8
Number of Patients	16	11	6	33	15	10	6	31	15	10	7	32

In my series, approximately half of the patients in the aureomycin group showed loss of appetite which was almost complete during the treatment period. For example, in the 5-8 day period, 48.5 per cent of the patients receiving aureomycin had loss of appetite, and the similar figures for chloramphenicol and control groups were 28.1 per cent and 16.1 per cent, as is shown in Table 20. During the second week in hospital, the appetite returned to normal in the patients treated with aureomycin. It would appear that aureomycin causes loss of appetite. This fact was not influenced by the duration of the illness before treatment was commenced.

Table 20.

Patients in whom Loss of Appetite was noted in each Four-Day Period, divided according to Treatment Groups

Treatment Group	Cases Observed		1-4 Days		5-8 Days		9-12 Days		Over 12 Days	
	No.	%	No.	%	No.	%	No.	%	No.	%
Control	31	100	7	22.9	5	16.1	3	9.7	1	3.3
Aureomycin	33	100	17	51.8	16	48.5	7	21.1	2	6.1
Chloramphenicol	32	100	12	37.5	9	28.1	3	9.4	0	0
All Patients	96	100	36	37.5	30	31.2	13	13.5	3	3.1

Bowel Movements. Looseness of stools was noted in eight patients, four in the aureomycin group, three in the chloramphenicol group, and two in the control group. In four of these patients the diarrhoea was present on admission and was probably a non-specific enteritis unassociated with whooping cough. A further two patients, aged six months and seven months, had transient diarrhoea which appeared to be related to dentition upset. In the remaining two patients there did appear to be an association with whooping cough. One of

these patients, aged two years, was admitted with the diagnosis "clinical dysentery". Paroxysmal cough became obvious five days after admission to hospital. The diarrhoea ceased soon after the paroxysmal cough became established. Moderately severe diarrhoea occurred on the 15th day of observation in a child who was severely ill with whooping cough complicated with bronchopneumonia and atelectasis. In no case was diarrhoea due to antibiotic therapy.

The Paroxysmal Cough and Expectoration.

The numbers and severity of the paroxysmal coughs in each case will be discussed in the next chapter. A thick mucus expectoration following the cough is common in many whooping cough patients and is generally considered to be a normal occurrence in the illness. Clinically detectable expectoration was noted in 55.2 per cent of the 96 whooping cough patients, 62.5 per cent in the chloramphenicol group, 45.5 per cent in the aureomycin group, and 58.1 per cent in the control group, as is shown in Table 21.

Table 21.

Patients in whom Mucoid Expectoration following Paroxysmal Coughing was noted (in 4-day Periods), divided according to Treatment Groups.

Treatment Group	Total Cases Observed	1-4 Days	5-8 Days	9-12 Days	13-16 Days	Over 17 Days
Control.....	31	18	17	14	11	9
Per cent	100	58.1	54.8	45.1	35.5	25.8
Aureomycin	33	15	15	12	9	7
Per cent	100	45.5	45.5	36.6	27.3	21.2
Chloramphenicol	32	20	16	12	2	2
Per cent	100	62.5	50.0	37.5	6.3	6.3
All Patients	96	53	48	38	22	18
Per cent	100	55.2	50.0	39.5	22.9	18.8

When the amount of expectoration is considered in each 4-day period it is noted that the expectoration lessens more quickly in the chloramphenicol patients. For example, on days 13-16, expectoration was present in 35.5 per cent of controls, 27.3 per cent of aureomycin treated patients, and 6.3 per cent of patients treated with chloramphenicol. When the amount of expectoration was compared with the records of clinical examinations, it was discovered that, in many instances during the treatment period, chloramphenicol patients appeared to develop a looser and more productive cough. Treatment by chloramphenicol may have been responsible for the speedier eradication of expectoration from the bronchial tree.

Three patients who developed a purulent expectoration will be discussed under complications.

Whooping.

The number of times each child whooped during each paroxysm was noted, and it was hoped that it might be possible to get an indication as to the severity of the paroxysmal cough from the number of whoops. There were, however, great differences in whooping among the patients. For example, one child whooped 527 times during 18 paroxysms in a 24-hour period. This was an average of 29.3 whoops during each paroxysm. Other children only whooped occasionally, and did not whoop at every inspiration during a paroxysm. Some children did not whoop at all during the entire course of the illness.

For the purpose of analysing the findings as regards whooping, I have placed each child into one of the following three categories:-

(a) Absent: No whoops observed during the entire 21-day observation period.

(b) Established: Patients in whom ten or more whoops per day were recorded on at least five successive days of observation.

(c) Occasional: Patients in whom whoops have been recorded but were insufficient to satisfy the above criteria of being established.

As is shown in Table 22, for all patients, whooping was absent in 47.8 per cent of patients, occasional in 18.9 per cent of the patients, and established in 33.3 per cent. of patients. There was no appreciable difference in the incidence between the treatment groups.

Table 22.

Incidence of "whooping" in 96 Whooping Cough Patients, divided according to Treatment Groups, and indicating whether "whooping" was Absent, Occasional, or Established.

Incidence of "whooping"	Control Group	Aureo-mycin Group	Chloram-phenicol Group	All Patients	
				Number	Per cent
Absent	15	16	15	46	47.8
Occasional	4	7	7	18	18.9
Established	12	10	10	32	33.3
Total	31	33	32	96	100

When the incidence of whooping was considered in relation to the ages of the patients, it was discovered that age bears a definite relationship to whooping. For the age-group 0-1 year, whooping was present in 28.3 per cent of patients; for the age-group 1-3 years, whooping was present in 64.3 per cent of patients; and in the age-group 3-5 years, whooping was present in 89.5 per cent of patients, as is shown in Table 23. Established whooping was noted in 63.2 per cent of patients aged 3-5 years, 45.0 per cent of patients aged

1-3 years, and 13.1 per cent of patients aged 0-1 year. These figures suggest that older patients tend to whoop more frequently than do patients under 1 year of age.

Table 23.

Incidence with Percentages of "whooping" in 96 Whooping Cough Patients, divided according to Treatment Groups and indicating whether "whooping" was Absent, Occasional or Established.

Incidence of "whooping"	AGE: 0-1 year		AGE: 1-3 years		AGE: 3-5 years	
	Number	Per cent	Number	Per cent	Number	Per cent
Absent	33	71.7	11	35.7	2	10.5
Occasional	7	15.2	6	19.3	5	26.3
Established	6	13.1	14	45.0	12	63.2
Total	46	100	31	100	19	100

Cyanosis.

Cyanosis was observed in nine patients, seven of whom were severely ill and two of whom were moderately ill. In seven cases, cyanosis was present only during the paroxysmal cough and was, on the whole, slight. One patient developed continuous cyanosis which became worse during paroxysmal coughing and persisted for seven days until death. The other case was one in which extensive atelectasis arose late in the illness. The cyanosis in this patient was slight and became worse during the paroxysmal cough. It lasted for seven days and the patient made a good recovery.

Other Signs.

Haemorrhage. Haemorrhagic phenomena are described as being characteristic during the paroxysmal stage. Lapin (1943) states that "subconjunctival haemorrhages and epistaxis are frequent." Other authorities, who include Christie (1945), Harries and Mitman (1947), Joe (1947) and Top (1947), make

similar statements. The only case in my series which exhibited this phenomenon was a male child aged four years who developed bilateral subconjunctival haemorrhages. In a personal series of 300 patients observed over the years 1950 to 1952, I have only seen one other case of haemorrhage and that was one of epistaxis. In my opinion, haemorrhages do not occur in whooping cough as frequently nowadays as they did in the past, possibly due to a lessening severity of the disease.

Ulceration of the Fraenum. This sign receives prominence in most of the standard text-books of infectious diseases, In my opinion it is uncommon, having been noted only once in the series described (a female child aged two years six months), and three times in a personal series of 300 cases observed over the years 1950-52.

Examination of the Chest.

Generally speaking, uncomplicated cases of whooping cough reveal no gross abnormality on physical examination of the chest. A degree of simple bronchitis may be noted in the early stages of the disease, and, in the later stages, temporary atelectasis may be noted. Emphysema may be present but is difficult to detect on physical examination, especially in young children.

The numbers of children who revealed no abnormality on physical examination of the chest in each 4-day period is shown in Table 24. As each successive 4-day period passed fewer and fewer children exhibited abnormal physical signs. In the control series 64.5 per cent had some degree of abnormality at the start of the trial and only 7.7 per cent had some abnormality after 20 days. This return to normality was markedly accelerated in these cases under treatment with chloramphenicol where 46.5 per cent showed abnormalities of the chest at

the start of the trial but only 12.5 per cent after 12 days, and only 6.3 per cent after 20 days. Aureomycin seemed to have no effect in accelerating the return to normality. The rate at which chloramphenicol caused a return to normal is marked, and the difference from the control series is significant.

Table 24

Numbers of Patients in whom Abnormal Physical Signs in the Chest were Absent, divided according to Treatment Groups (in 4-Day Periods).

Treatment Group		1-4 Days	5-8 Days	9-12 Days	13-16 Days	17-20 Days	Over 20 Days
Control	- 31 Patients	11	13	16	19	21	28
	Per cent	35.5	41.9	51.6	61.6	67.7	92.3
Aureomycin	- 33 Patients	14	18	20	23	24	25
	Per cent	42.1	54.2	60.6	69.7	72.7	75.8
Chloramphenicol	- 32 Patients	17	19	23	28	30	30
	Per cent	53.5	59.4	61.9	87.5	93.7	93.7
All Patients (96)		42	50	59	70	75	83
	Per cent	43.7	52.1	61.5	72.9	78.1	86.5

Clinical Assessment of the Effect of Treatment on the Course of the Illness.

An attempt was made to assess the clinical condition of the patient after seven days of treatment. This was based on the ward sister's and my own clinical impression of the case on the eighth day of observation. As none of us knew which case was in the control group and which was receiving treatment, these impressions are considered to be of value.

The clinical assessment was based on four categories - no improvement or worse than on admission, slight, good, or dramatic improvement.

As is shown in Table 25, cases under treatment fared better than the control group, where, for example, 37.5 per cent of the patients treated with

Table 25.

Results of the Clinical Assessment of the Effect of the 7-Day Treatment Period on the Course of the Illness - Divided according to Duration of Illness prior to Admission.

Degree of Improvement	Early Cases			Intermediate Cases			Late Cases			All Patients		
	Ch. No. %	C. No. %	A. No. %	Ch. No. %	C. No. %	A. No. %	Ch. No. %	C. No. %	A. No. %	Ch. No. %	C. No. %	A. No. %
Nil or Worse	1 11.1	5 55.6	2 22.2	6 65.3	8 57.1	4 25.0	2 33.3	5 62.5	1 12.5	9 28.1	18 58.0	7 21.2
Slight	4 44.4	2 22.2	4 44.4	3 17.6	2 14.3	5 31.3	1 16.7	2 25.0	1 12.5	8 25.0	6 19.4	10 30.3
Good	4 44.4	2 22.2	3 33.3	5 29.4	4 28.5	7 43.7	3 50.0	1 12.5	5 62.5	12 37.5	7 22.6	15 45.4
Dramatic	0 0	0 0	0 0	3 17.6	0 0	0 0	0 0	0 0	1 12.5	3 9.4	0 0	1 3.0
Total	9 100	9 100	9 100	17 100	14 100	16 100	6 100	8 100	8 100	32 100	31 100	33 100

Ch. = Chloramphenicol
C. = Control
A. = Aureomycin

chloramphenicol and 45.4 per cent of those treated with aureomycin had improved to an extent judged to be "good", as compared with only 22.6 per cent of the control series. Improvement judged as "dramatic" was only noticed in four patients, of whom three were treated with chloramphenicol and one was treated with aureomycin.

Relapsed Cases.

Five patients treated with chloramphenicol relapsed after cessation of the treatment. This will be discussed fully in the next chapter.

Total Residence in Hospital.

It is well known that whooping cough patients require to be hospitalized for a longer period than do patients suffering from other common infectious diseases. Thus, it was hoped that if an effective treatment of the disease could be evolved it would result in a shorter period of hospitalization with a consequent saving of hospital beds and diminution of the always attendant risks of cross infection. An analysis was made of the effect of treatment on the length of stay of whooping cough patients in hospital.

The average length of stay in hospital was 4.7 weeks for control cases, 5.2 weeks for cases treated with aureomycin, and 4.3 weeks for cases treated with chloramphenicol. After the fifth week in hospital 55.0 per cent of control cases, 41.6 per cent of cases treated with aureomycin, and 75.0 per cent of cases treated with chloramphenicol had been dismissed, as is shown in Table 26. In this restricted series of patients selected at random, the average length of stay in hospital was less in the chloramphenicol group and greater in the aureomycin group than in the control group.

Table 26.

Frequency Distribution of Total Residence in Hospital of 96 Whooping Cough Patients.

Length of Stay in Hospital (Weeks)	Control Group		Aureomycin Group		Chloramphenicol Group		All Patients	
	No.	%	No.	%	No.	%	No.	%
3 -	11	35.5	12	36.4	12	37.5	35	36.5
4 -	6	19.5	5	15.2	12	37.5	23	23.8
5 -	4	12.9	4	12.1	1	3.1	9	9.5
6 -	4	12.9	3	9.1	3	9.4	10	10.6
7 -	3	9.6	3	9.1	0	-	6	6.2
8 -	3	9.6	1	3.0	1	3.1	5	5.1
Over 9	0	-	4	12.1	2	6.2	6	6.2
Deaths	0	-	1	3.0	1	3.1	2	2.1
Total	31	100	33	100	32	100	96	100

Summary.

The various clinical manifestations of the disease have been given and discussed.

Temperature, pulse, and respiration rates were not greatly affected by the illness.

A catarrhal condition of the nasal mucosa was present in 56.3 per cent of patients. This tended to clear up more quickly in patients treated with chloramphenicol than in control patients.

Vomiting was a variable symptom and, during the period when treatment was being administered, it occurred more frequently in patients who were receiving antibiotic therapy than it did in the control patients. Generally speaking, early cases vomited more frequently than did late cases, and children over three years of age vomited more frequently than did the younger children. Aureomycin caused loss of appetite in approximately half of the patients treated.

Patients who received chloramphenicol therapy were noted to have a more productive cough and a looser expectoration of mucus than did control patients and patients receiving aureomycin.

Great variation was discovered in the number of times each child whooped. Whooping was more frequently present in children in the older age groups than in childreh under one year of age. There were 47.8 per cent of patients who did not whoop at all.

The average length of stay in hospital of patients treated with chloramphenicol was less than that of those in the control group.

CHAPTER 8.

EFFECT OF THE ANTIBIOTICS USED ON THE PAROXYSMAL COUGH

The Number of Paroxysms.

The average number of paroxysms per case was calculated separately for each of the 21 days of observation. The results for each day are shown in Figures 8, 9, 10 and 11, and the tables from which these graphs have been compiled appear in the Appendix.

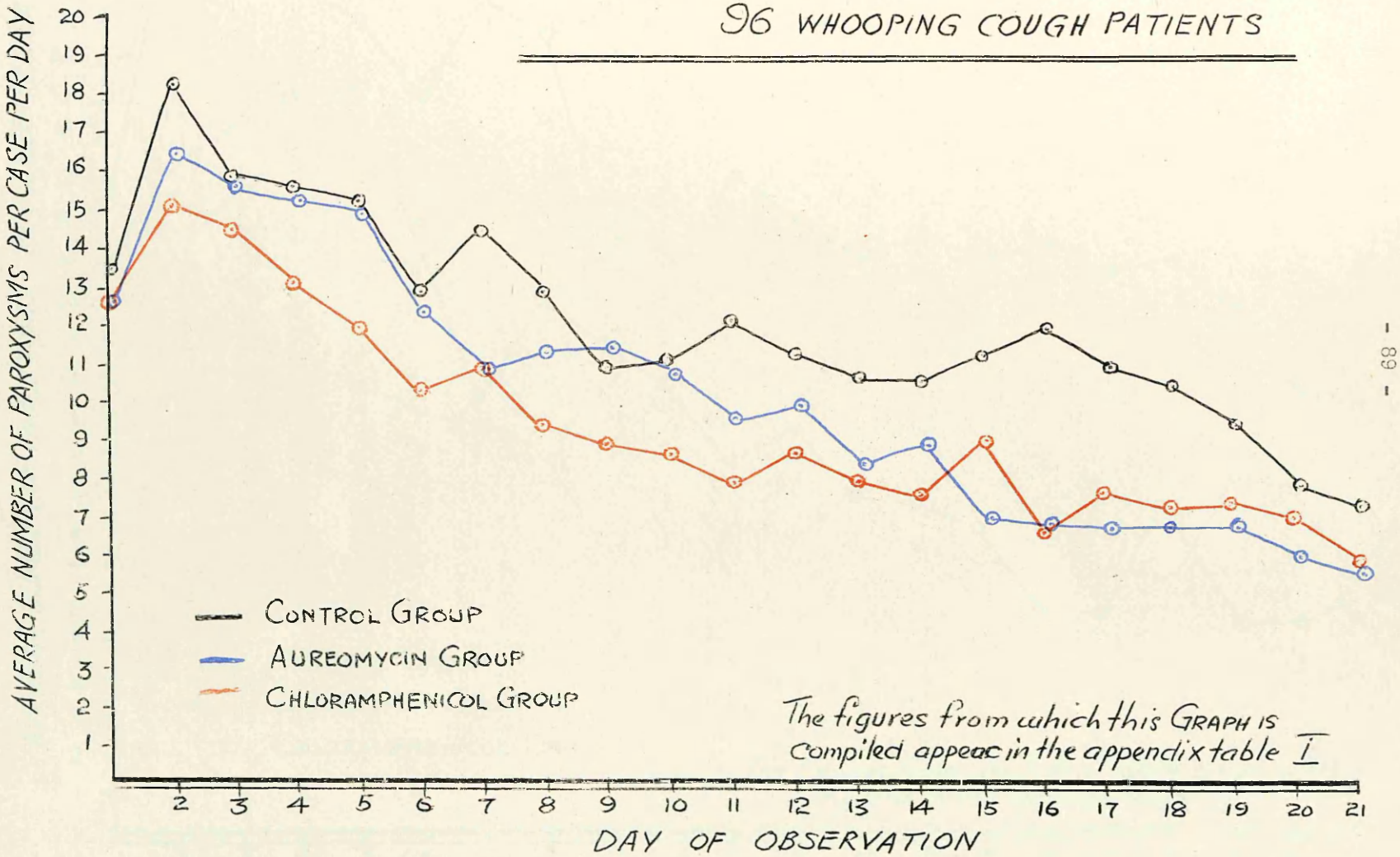
Generally speaking, when all the patients in the trial were considered, the average number of paroxysms per case per day was less in the aureomycin and chloramphenicol groups than in the control group. This is illustrated in Figure 8. On the 8th day of observation, the average difference between the control group and the aureomycin group was 1.8 paroxysms, and between the control group and the chloramphenicol group was 3.8 paroxysms. It appeared, therefore, that treated patients fared little better than these who acted as controls.

Analysis by Duration of Illness prior to Admission to Hospital.

The average number of paroxysms per case in the early, intermediate, and late cases are shown in Figures 9, 10 and 11 respectively. For the early cases the average number of paroxysms per case was consistently less in the aureomycin and chloramphenicol groups than in the control group. For example, on the 8th, 12th and 16th days the average differences between the control group and the aureomycin group were 6.6, 5.2 and 9.8 paroxysms respectively. Between the control group and the chloramphenicol group the average differences on the same days were 10.6, 8.2 and 9.2 paroxysms. For the intermediate and late cases there was no appreciable difference in the average number of paroxysms between treated and control patients (Figures 10 and 11).

It would appear, therefore, that treatment with chloramphenicol and aureomycin is effective in reducing the number of paroxysms only if the treatment

FIG 8. THE AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY IN THE 3 TREATMENT GROUPS :- 96 WHOOPING COUGH PATIENTS



The figures from which this GRAPH IS compiled appear in the appendix table I

FIG. 9. THE AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY IN THE 3 TREATMENT GROUPS – 27 EARLY CASES

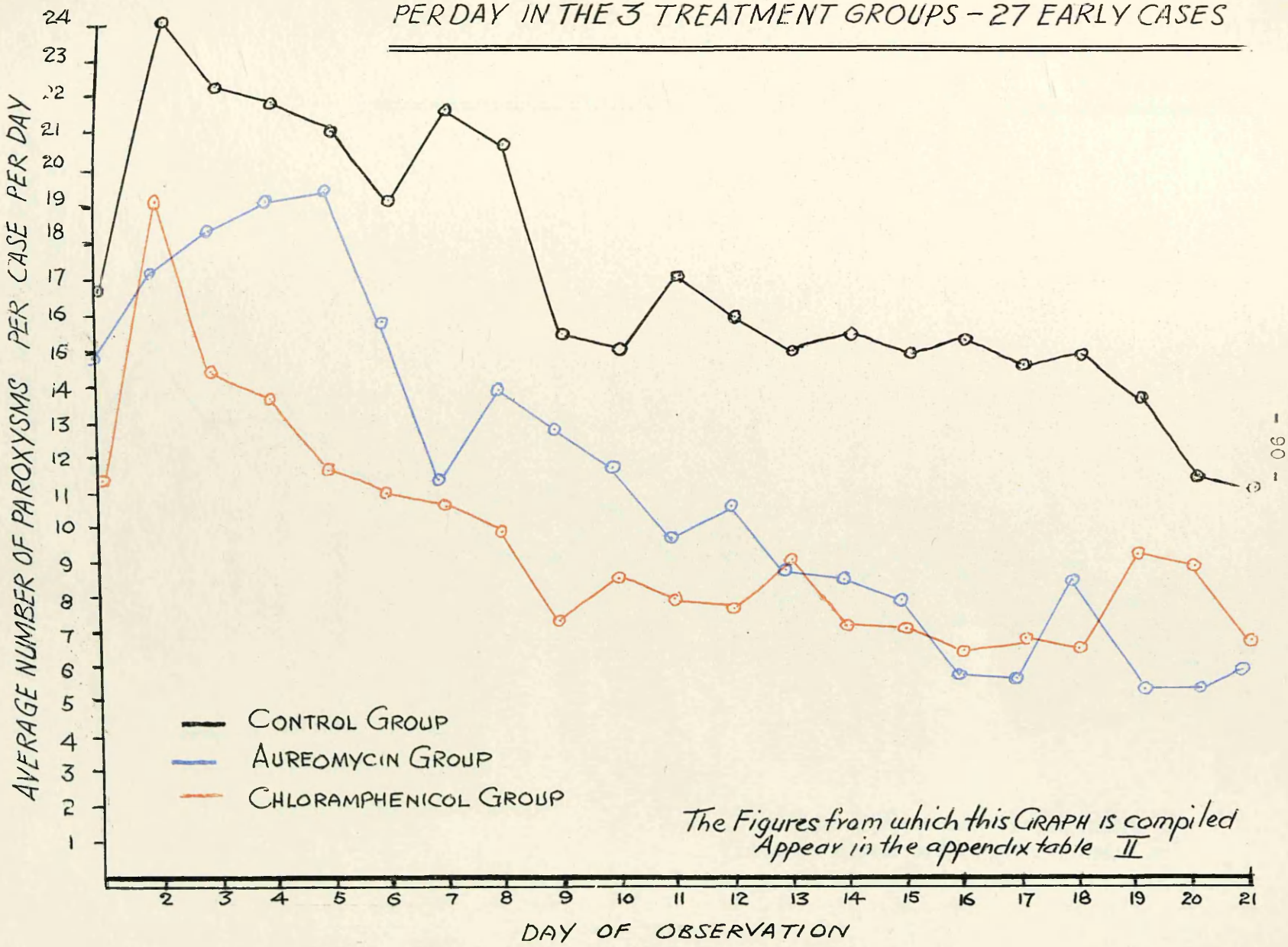
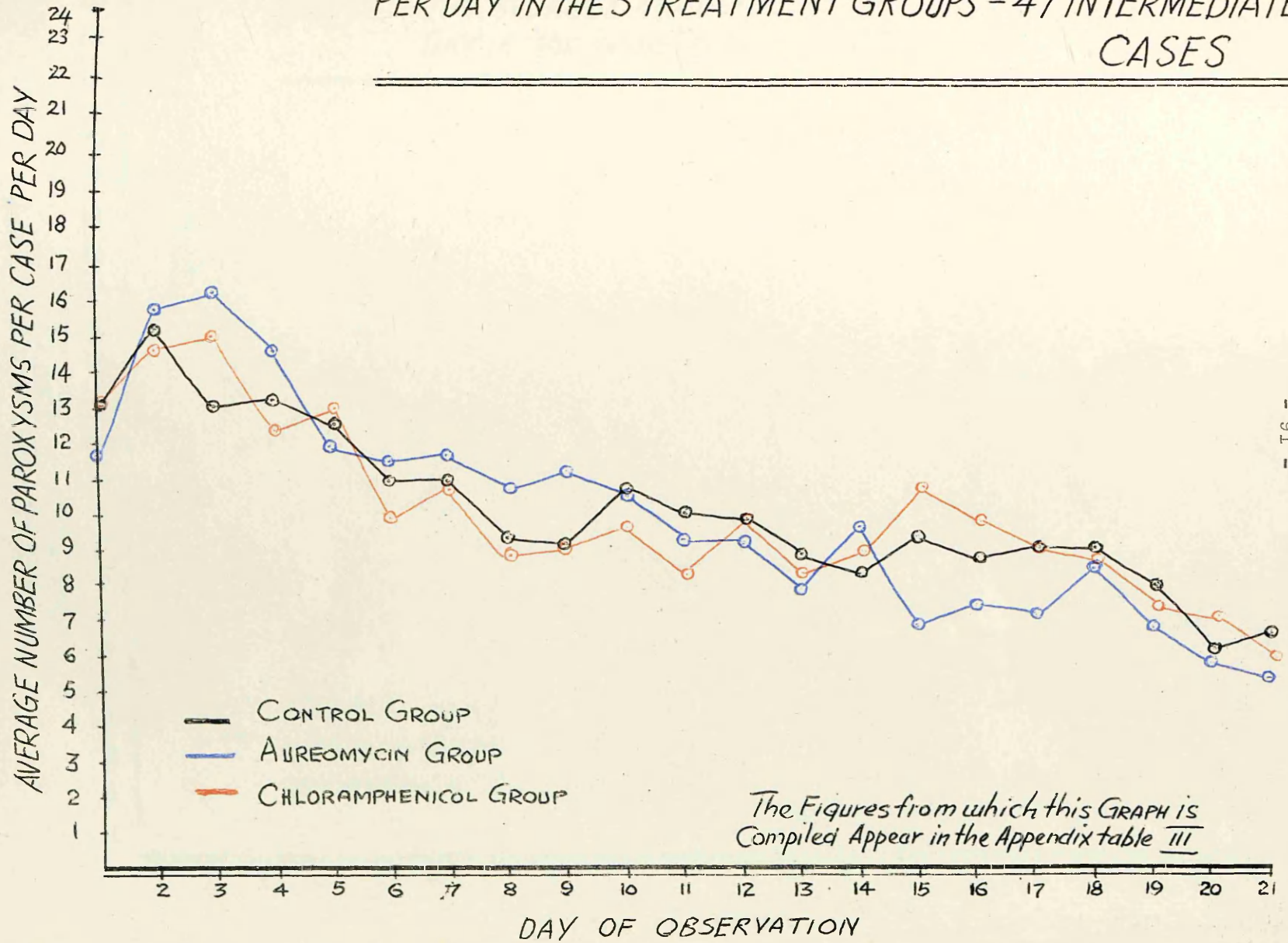
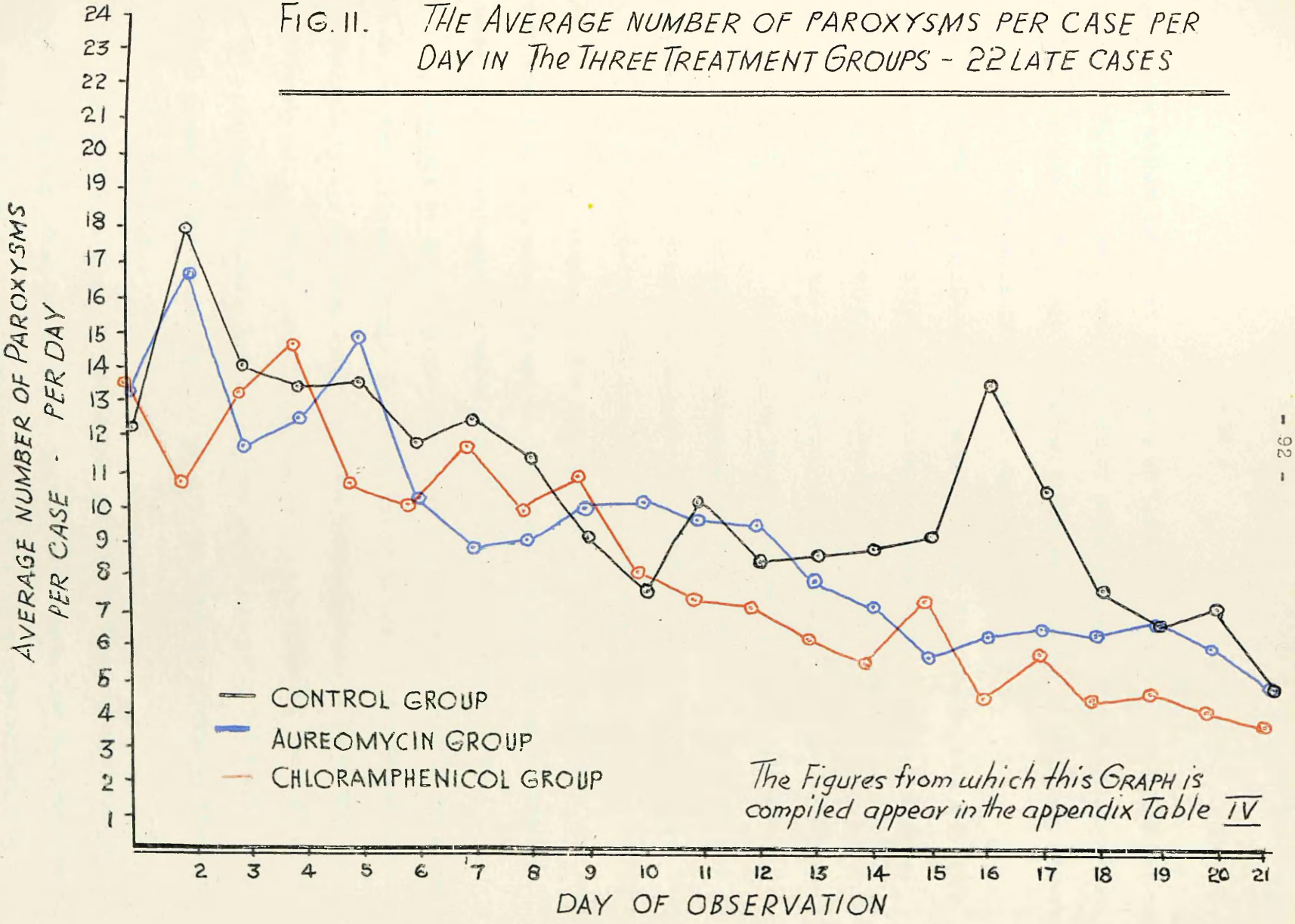


FIG. 10. THE AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY IN THE 3 TREATMENT GROUPS – 47 INTERMEDIATE CASES



The Figures from which this GRAPH is Compiled Appear in the Appendix table III

FIG. 11. THE AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY IN THE THREE TREATMENT GROUPS - 22 LATE CASES



The Figures from which this GRAPH is compiled appear in the appendix Table IV

is started within the first eight days of illness. This is further illustrated in Table 27, where the average numbers of paroxysms per case per day are shown in 4-day periods. The only consistent difference between the antibiotic treated cases and the controls is in the early cases.

A further analysis was then made by calculating for the 2nd, 8th, 14th and 20th days of observation the numbers and percentages of cases with 0-9, 10-19, and 20 or more paroxysms (Tables 28, 29, 30 and 31). By this method also the difference between the control group and the antibiotic treated group was greater in the early cases. On the 14th day the percentage of patients with 0-9 paroxysms was 66.7 per cent for chloramphenicol treated cases, 77.8 per cent for aureomycin treated cases, and 22.2 per cent for control cases (Table 29). However, when the intermediate and late cases were considered there was no similar difference. For example, by the 14th day the percentages of intermediate cases with more than nine paroxysms was 43.7 per cent for chloramphenicol treated cases, 43.8 for aureomycin treated cases, and 35.7 for control cases.

Analysis by Age. At the time of writing there has been little attempt to assess the influence of age on the antibiotic treatment of whooping cough. An analysis by age was made on patients who were estimated as being moderately or severely ill. There were 32 patients in the age-group 0-1 year, 21 patients in the age-group 1-3 years, and 14 patients in the age-group 3-5 years. The average number of paroxysms per case per day for these age-groups is shown in Figures 12, 13 and 14.

Reference to Figure 12 indicates that the frequency of the paroxysms decreased rapidly after two to three days in the patients aged 0-1 year treated with aureomycin and chloramphenicol. On the 8th day of observation, the

Table 27.

The Average Numbers of Paroxysms per Case per Day in 4-Day Periods

	Days 1-4			Days 5-8			Days 9-12			Days 13-16			Days 17-20		
	Ch.	C.	A.	Ch.	C.	A.	Ch.	C.	A.	Ch.	C.	A.	Ch.	C.	A.
All Cases															
Av. No. of Paroxysms per Case per Day	13.8	15.2	14.7	10.3	13.9	12.3	8.4	11.4	10.4	7.7	11.1	7.8	7.1	9.7	6.5
Difference ...		1.4	0.5		3.6	1.6		3.0	1.0		3.4	3.3		2.6	3.2
Early Cases															
Av. No. of Paroxysms per Case per Day	14.7	21.2	17.4	10.9	20.6	15.2	7.9	15.9	11.3	7.5	15.3	7.9	7.9	13.8	6.5
Difference ...		6.5	3.8		9.7	5.4		8.0	4.6		7.8	7.4		5.9	7.3
Intermediate Cases															
Av. No. of Paroxysms per Case per Day	13.8	13.7	14.5	10.5	11.0	11.6	9.0	10.0	10.0	9.8	9.0	7.9	7.9	8.6	7.1
Difference ...		0.1	0.8		0.5	0.6		1.0	-		0.8	1.1		0.7	1.5
Late Cases															
Av. No. of Paroxysms per Case per Day	12.4	14.3	13.4	10.0	14.7	10.5	7.2	8.7	9.7	5.1	9.8	6.6	4.1	7.8	6.2
Difference ...		1.9	0.9		4.7	4.2		1.5	1.0		4.7	3.2		3.7	1.6

Ch. = Chloramphenicol Group C. = Control Group A. = Aureomycin Group

Table 28.

Number and Percentages of Patients with 0-9, 10-19 and 20 or more Paroxysms on the 2nd, 8th, 14th and 20th Days of Observation - All Cases

Number of Paroxysms	Day 2						Day 8						Day 14						Day 20					
	Ch.		C.		A.		Ch.		C.		A.		Ch.		C.		A.		Ch.		C.		A.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-9	7	21.9	6	19.4	8	24.2	19	59.4	14	45.2	18	54.5	21	67.7	16	51.6	22	66.7	25	80.6	19	61.3	26	81.2
10-19	19	59.4	12	38.7	15	45.5	11	34.4	11	35.5	12	36.4	9	29.0	13	41.9	19	27.3	4	12.9	11	35.5	6	18.8
20 and Over	6	18.8	13	41.9	10	30.3	2	6.3	6	19.4	3	9.1	1	3.2	2	6.5	2	6.1	2	6.5	1	3.2	0	0
Number of Patients Observed	32	100	31	100	33	100	32	100	31	100	33	100	31	100	31	100	33	100	31	100	31	100	32	100

Ch. = Chloramphenicol
C. = Control
A. = Aureomycin

Table 29.

Number and Percentages of Patients with 0-9, 10-19 and 20 or More Paroxysms on the 2nd, 8th, 14th and 20th Days of Observation - Early Cases

Number of Paroxysms	Day 2						Day 8						Day 14						Day 20					
	Ch.		C.		A.		Ch.		C.		A.		Ch.		C.		A.		Ch.		C.		A.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-9	1	11.1	0	0	2	22.2	8	88.9	1	11.1	4	44.4	6	66.7	2	22.2	7	77.8	7	77.8	3	33.3	8	88.8
10-19	5	55.6	4	44.4	4	44.4	1	11.1	4	44.4	3	33.3	3	33.3	5	55.6	2	22.2	1	11.1	5	55.6	1	11.1
20 and Over	3	33.3	5	55.6	3	33.3	0	0	4	44.4	2	22.2	0	0	2	22.2	0	0	1	11.1	1	11.1	0	0
Number of Patients Observed	9	100	9	100	9	100	9	100	9	100	9	100	9	100	9	100	9	100	9	100	9	100	9	100

Ch. = Chloramphenicol
C. = Control
A. = Aureomycin

Table 30.

Number and Percentages of Patients with 0-9, 10-19 and 20 or More Paroxysms on the 2nd, 8th, 14th and 20th Days of Observation - Intermediate Cases

Number of Paroxysms	Day 2						Day 8						Day 14						Day 20					
	Ch.		C.		A.		Ch.		C.		A.		Ch.		C.		A.		Ch.		C.		A.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-9	4	23.5	6	42.9	5	31.3	11	64.7	9	64.3	9	56.3	9	56.3	9	64.3	9	56.3	12	75.0	11	78.6	13	86.7
10-19	10	58.8	3	21.4	6	37.5	5	29.4	4	28.6	6	37.5	6	37.5	5	35.7	5	31.3	3	18.8	3	21.4	2	13.3
20 and Over	3	17.6	5	35.7	5	31.3	1	5.9	1	7.1	1	6.2	1	6.2	0	0	2	12.5	1	6.2	0	0	0	0
Number of Patients Observed	17	100	14	100	16	100	17	100	14	100	16	100	16	100	14	100	16	100	16	100	14	100	15	100

Ch. = Chloramphenicol
C. = Control
A. = Aureomycin

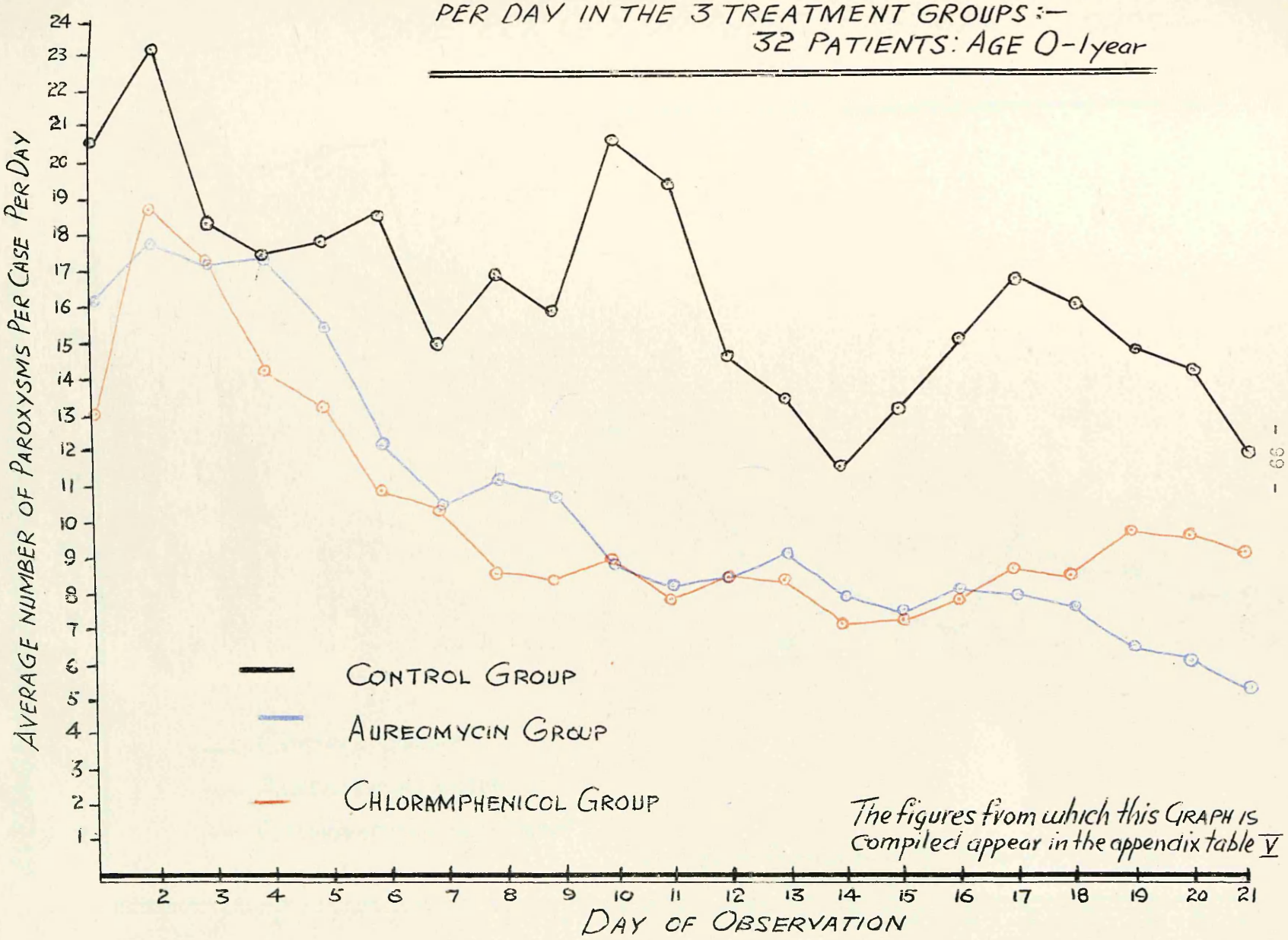
Table 31.

Number and Percentages of Patients with 0-9, 10-19 and 20 or More Paroxysms on the 2nd, 8th, 14th and 20th Days of Observation - Late Cases

Number of Paroxysms	Day 2						Day 8						Day 14						Day 20					
	Ch.		C.		A.		Ch.		C.		A.		Ch.		C.		A.		Ch.		C.		A.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-9	2	33.3	0	0	1	12.5	2	33.3	4	50.0	5	62.5	6	100	6	75.0	6	75.0	6	100	5	62.5	5	62.5
10-19	4	66.7	5	37.5	5	62.5	4	66.7	3	37.5	3	37.5	0	0	2	25.0	2	25.0	0	0	3	37.5	3	37.5
20 and Over	0	0	3	62.5	2	25.0	0	0	1	12.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Number of Patients Observed	6	100	8	100	8	100	6	100	8	100	8	100	6	100	8	100	8	100	6	100	8	100	8	100

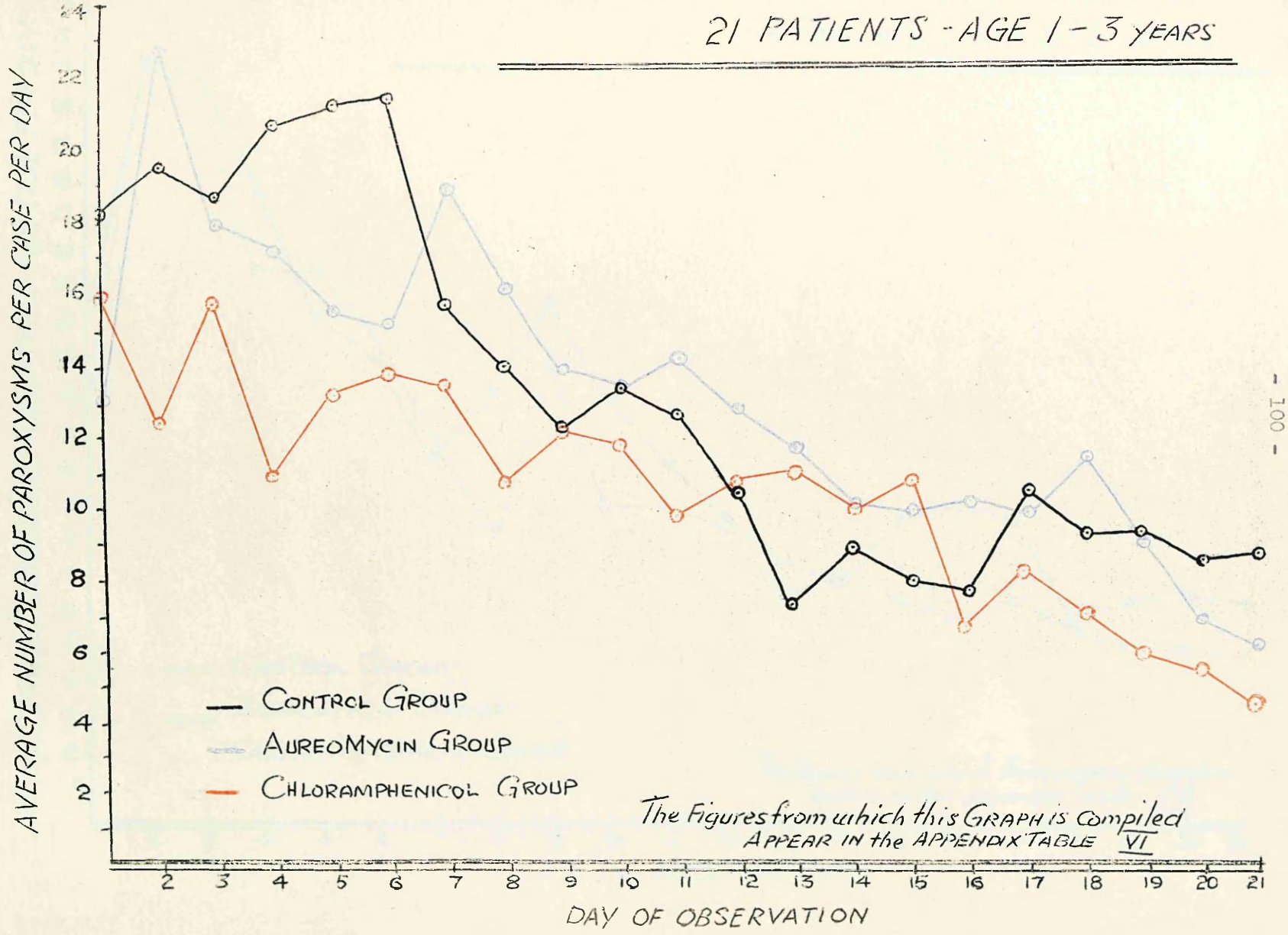
Ch. = Chloramphenicol
C. = Control
A. = Aureomycin

FIG. 12 THE AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY IN THE 3 TREATMENT GROUPS :— 32 PATIENTS: AGE 0-1 year



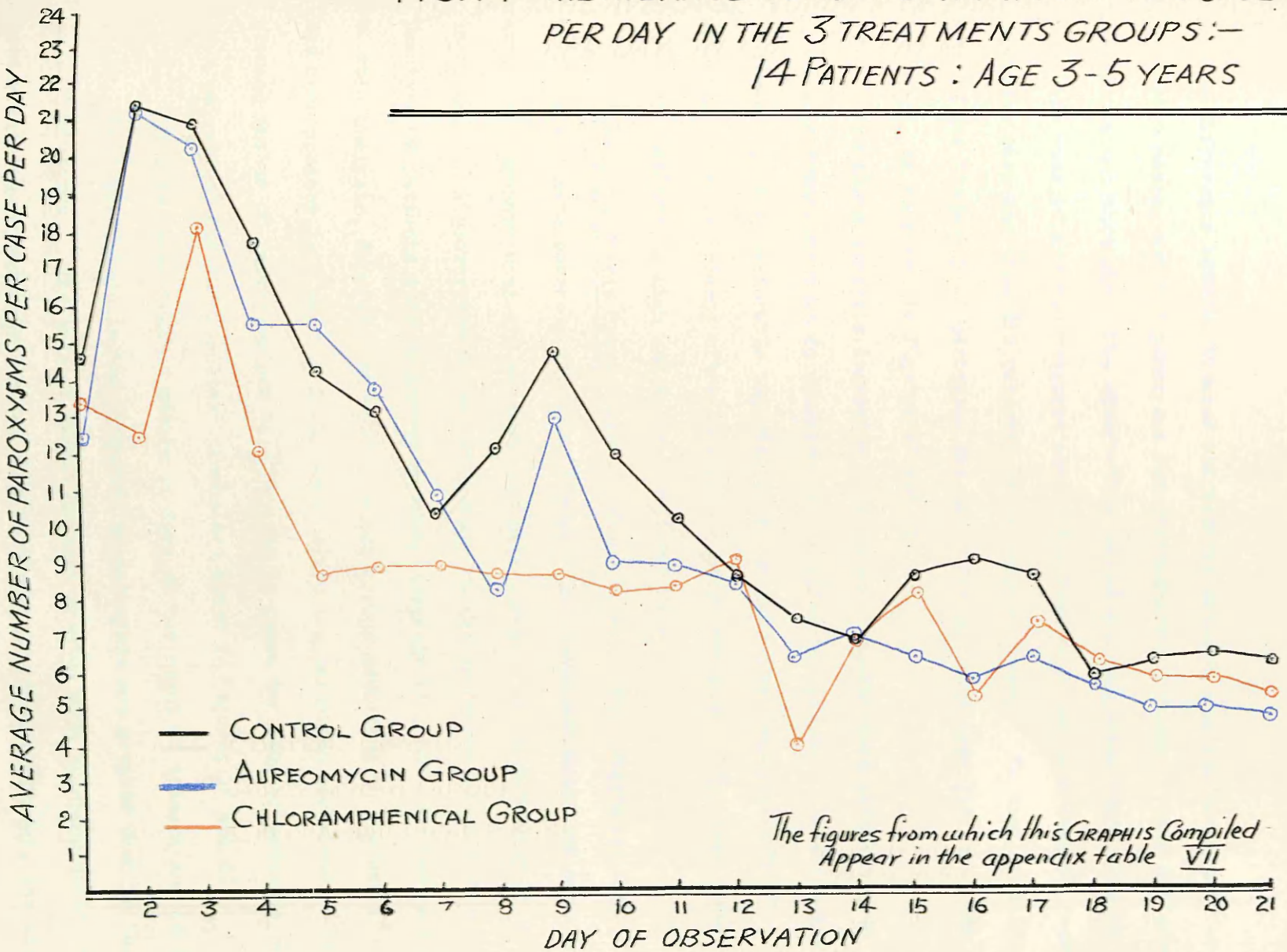
The figures from which this GRAPH IS compiled appear in the appendix table V

FIG. 13. THE AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY IN THE 3 TREATMENT GROUPS — 21 PATIENTS - AGE 1 - 3 YEARS



The Figures from which this GRAPH is Compiled APPEAR in the APPENDIX TABLE VI

FIG. 14 THE AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY IN THE 3 TREATMENTS GROUPS :— 14 PATIENTS : AGE 3-5 YEARS



The figures from which this GRAPH IS Compiled Appear in the appendix table VII

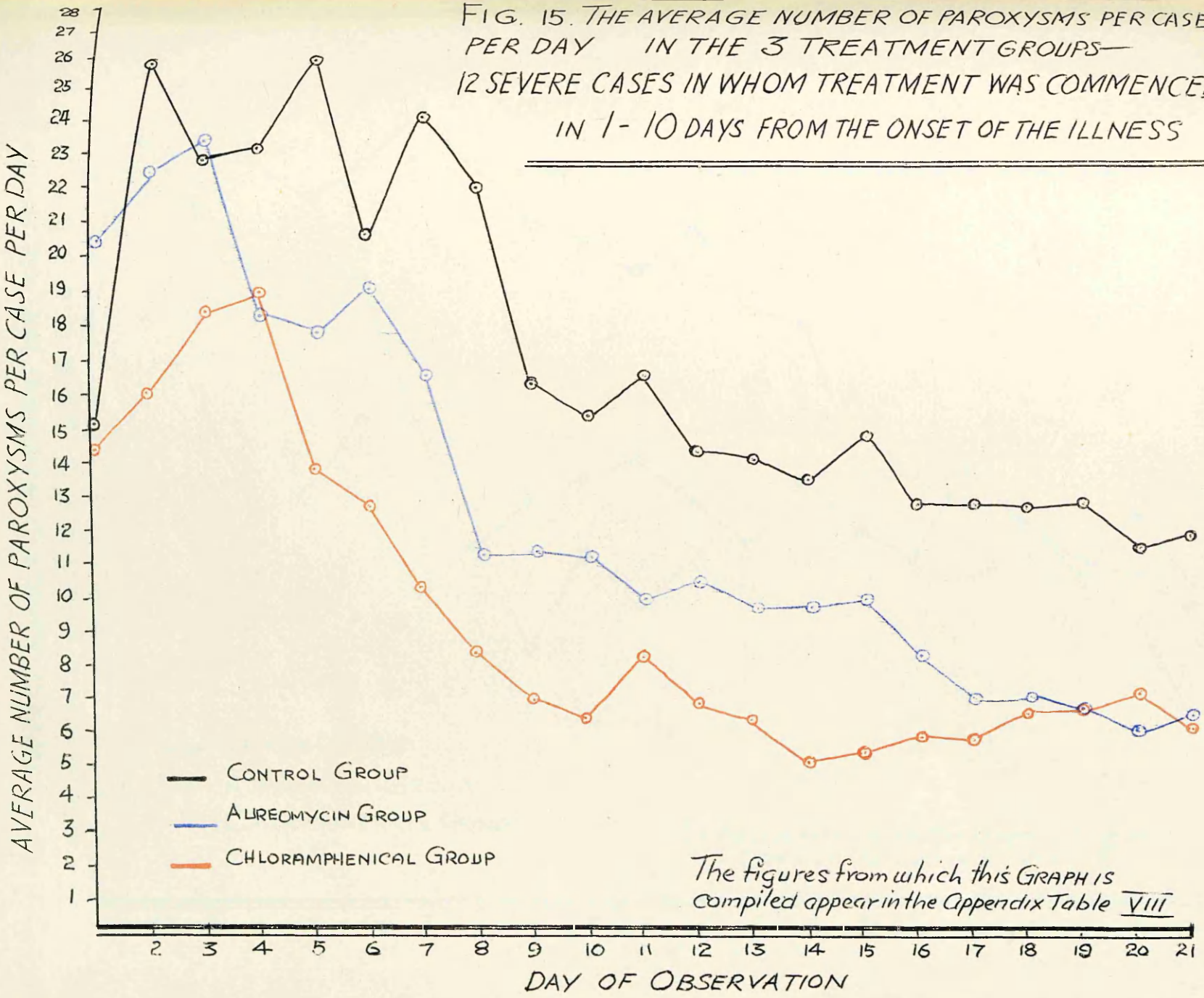
average difference between treated and control patients was 5.8 paroxysms for aureomycin cases, and 8.6 paroxysms for chloramphenicol cases. This difference was maintained throughout the observation period and suggested that patients under one year of age who received antibiotic treatment had considerably fewer paroxysms each day than did patients in the control group. No similar difference in the frequency of paroxysms was noted for patients aged 1-3 years and 3-5 years, as is shown in Figures 13 and 14.

The above analysis indicates that infants respond more favourably to antibiotic treatment than do children in the older age-groups. This finding is obviously of considerable importance as the pulmonary complications of whooping cough in infancy often remain as a permanent disability, and, moreover, the case fatality is high under the age of one year.

Analysis of the Severe Cases. Chang et al. (1950) suggested that patients who were severely ill when treatment was commenced benefited more from antibiotic therapy than did moderate and mild cases. It is obviously of great importance to discover the effect of therapy on the paroxysms in severe cases. Twenty-four patients were estimated as being severely ill, and, for the purpose of this analysis, they were divided into two groups according to whether illness had been present 1-10 days or 11-21 days before treatment was commenced. The average number of paroxysms per case per day in these two sets of patients have been calculated and the resultant graphs are shown in Figures 15 and 16.

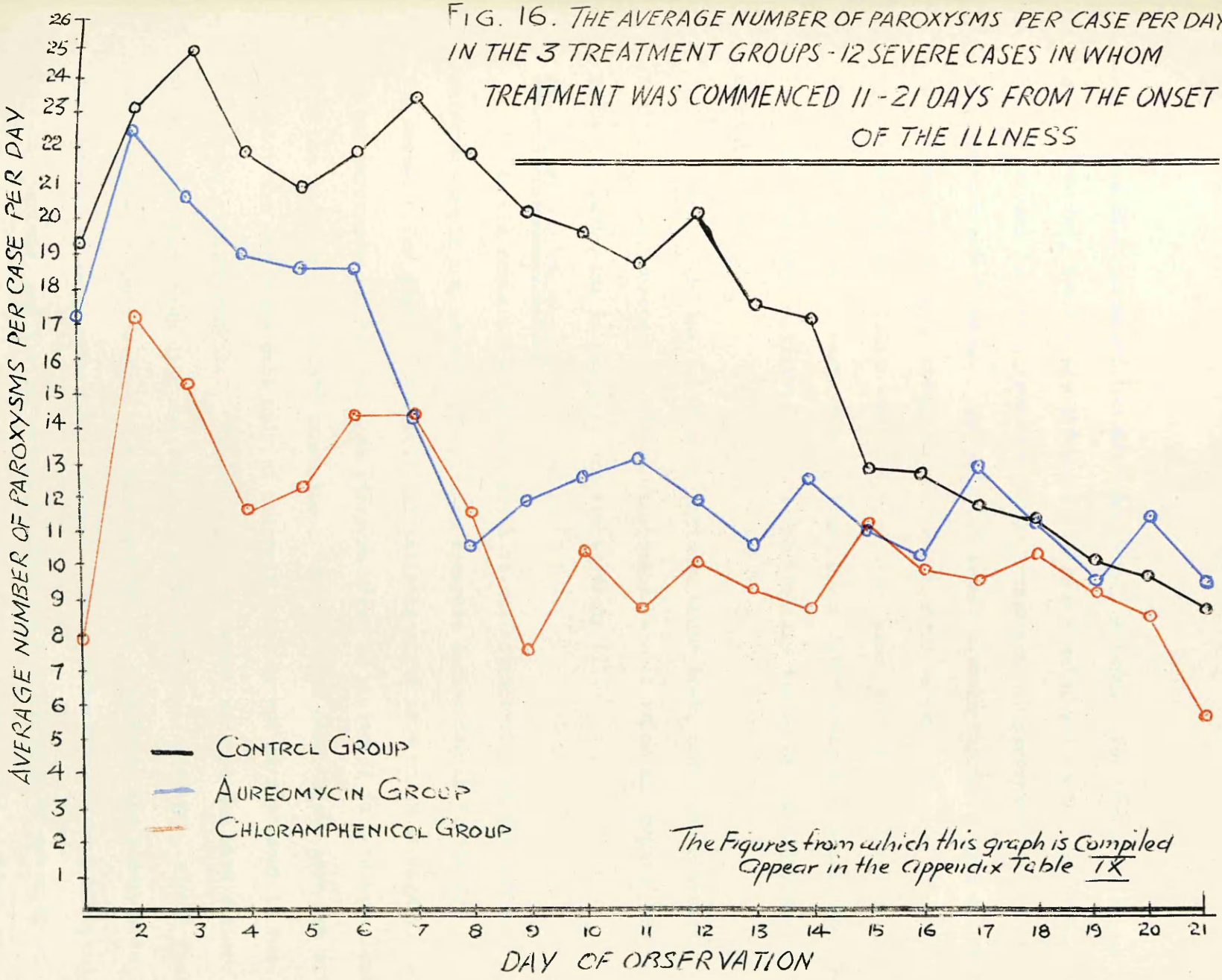
In both cases treated within 10 days of the onset of illness and in later cases, the distribution in the frequency of paroxysms was greater than in the control patients. The earlier cases who were treated with chloramphenicol fared better than these who were treated with aureomycin. On the 8th day, the average difference between treated and control patients was 10.5 paroxysms for aureomycin

FIG. 15. THE AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY IN THE 3 TREATMENT GROUPS— 12 SEVERE CASES IN WHOM TREATMENT WAS COMMENCED IN 1 - 10 DAYS FROM THE ONSET OF THE ILLNESS



The figures from which this GRAPH IS compiled appear in the Appendix Table VIII

FIG. 16. THE AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY IN THE 3 TREATMENT GROUPS - 12 SEVERE CASES IN WHOM TREATMENT WAS COMMENCED 11 - 21 DAYS FROM THE ONSET OF THE ILLNESS



The Figures from which this graph is Compiled appear in the Appendix Table IX

cases, and 13.5 paroxysms for Chloramphenicol patients. For the later cases on the 8th day, the average difference between treated and control patients was 11.0 paroxysms for the aureomycin treated cases and 9.9 paroxysms for the chloramphenicol treated cases. The main difference between the two graphs was that the average difference between treated and control patients was consistent throughout the observation period for earlier cases, and for the later cases, the average number of paroxysms for treated and control patients became comparable about the 14th day of illness. This was probably due to natural recovery in the control cases.

Despite the small number of patients under test, there was a strong indication that aureomycin and chloramphenicol are of value in reducing the number of paroxysms in patients who are severely ill.

The Severity of Paroxysms.

At the commencement of the trial it was considered that the number of paroxysms would not necessarily give an accurate indication as to the progress of the cases. For example, severely ill patients might have on an average as few as ten paroxysms per day but each paroxysm might be prolonged to such an extent that the child would be left exhausted. On the other hand, cases were met with in which the paroxysms were only of moderate severity and were present in comparatively greater numbers. Therefore, it was arranged that the ward sister, who did not know which drug was being given to individual patients, should record each day during the observation period whether she considered the paroxysms in each case to be mild, moderate or severe. This information has been analysed in 4-day periods, and the percentage of cases in each category of severity of paroxysms are shown for all, early, intermediate, and late cases in Table 32.

Table 32.

Percentages of Cases where the Paroxysms were described as Absent or Mild, Moderate, or Severe (on 4-Day Periods).

Description of Paroxysms	Days 1-4			Days 5-8			Days 9-12			Days 13-16			Days 17-20		
	Ch.	C.	A.	Ch.	C.	A.	Ch.	C.	A.	Ch.	C.	A.	Ch.	C.	A.
All Cases:															
Absent or Mild..	12.5	14.5	16.7	32.0	17.7	26.5	61.3	39.5	39.4	62.1	51.1	63.3	70.2	58.9	71.1
Moderate	63.3	58.1	43.9	49.2	54.8	47.0	32.2	33.1	48.5	34.7	29.8	27.3	29.0	26.6	26.6
Severe	24.2	27.4	39.4	18.8	27.5	26.5	6.5	27.4	12.1	3.2	19.1	9.1	0.8	14.5	2.3
Early Cases:															
Absent or Mild .	11.1	11.1	16.7	30.6	13.9	33.3	61.1	25.0	38.9	66.7	27.8	52.7	77.8	44.4	75.0
Moderate	77.7	33.3	38.9	58.3	38.9	36.1	36.1	30.6	50.0	33.3	36.1	44.4	22.2	36.1	25.0
Severe	11.1	55.6	44.4	11.1	47.2	30.6	2.9	44.4	11.1	-	36.1	2.8	-	19.5	-
Intermediate Cases:															
Absent or Mild .	12.1	3.5	25.0	33.8	7.1	31.2	67.2	39.2	46.8	59.3	51.8	68.5	65.6	59.0	73.3
Moderate	48.4	82.0	43.8	42.6	76.8	50.0	23.4	42.8	45.8	34.2	37.5	25.0	32.7	33.9	25.0
Severe	39.5	14.5	31.2	23.6	16.1	18.8	9.4	17.8	9.4	6.5	10.7	6.5	1.7	7.1	1.7
Late Cases:															
Absent or Mild .	16.7	37.5	-	29.2	40.8	9.3	50.0	58.2	25.0	58.3	75.0	65.6	66.7	75.0	62.5
Moderate	83.3	43.8	50.0	54.2	34.2	50.0	50.0	16.8	56.2	41.7	9.3	15.7	33.3	3.1	31.3
Severe	-	18.7	50.0	16.6	25.0	40.8	-	25.0	18.8	-	15.7	18.8	-	21.9	6.2

Ch. = Chloramphenicol Group. C. = Control. A. = Aureomycin

The greater differences between the control group and the aureomycin treated and chloramphenicol treated groups were in the early cases. For example, the proportion of early control cases in which the paroxysms were described as being absent or mild increased from 11.1 per cent on days 1-4 to 44.4 per cent on days 17-20; whereas, in the treated cases during the same periods, the percentages increased from 11.1 to 77.8 for chloramphenicol treated cases, and from 16.7 to 75.0 for aureomycin treated cases. For patients with severe paroxysms, the percentage of control cases fell from 55.6 to 44.4 in days 1-4 and days 9-12 respectively; whereas in the same 4-day periods, the percentages were 44.4 and 11.1 for aureomycin treated caces.

For the Medical Research Council trial as a whole, it appeared that, with the exception of late cases, the drugs influenced the severity of the paroxysms to a greater extent than they affected the number of paroxysms. In my series the number of intermediate cases was not sufficiently large to draw a definite conclusion, but the general indication was that a similar effect took place.

Cough Index. It was felt when assessing the average number of daily paroxysms, insufficient value was given to the severity of the paroxysms. For example, a child who was severely ill might have very few paroxysms each day but each paroxysm may be extremely severe and leave the child exhausted. In order to give the effect of severity on the number of paroxysms a weighting device was originated, and this was called the "cough index". For the purpose of this analysis the number of daily paroxysms in each case was multiplied by the following arbitrary values according to the ward sisters' estimate of severity:-

Severe - 3. Moderate - 2. Mild - 1.

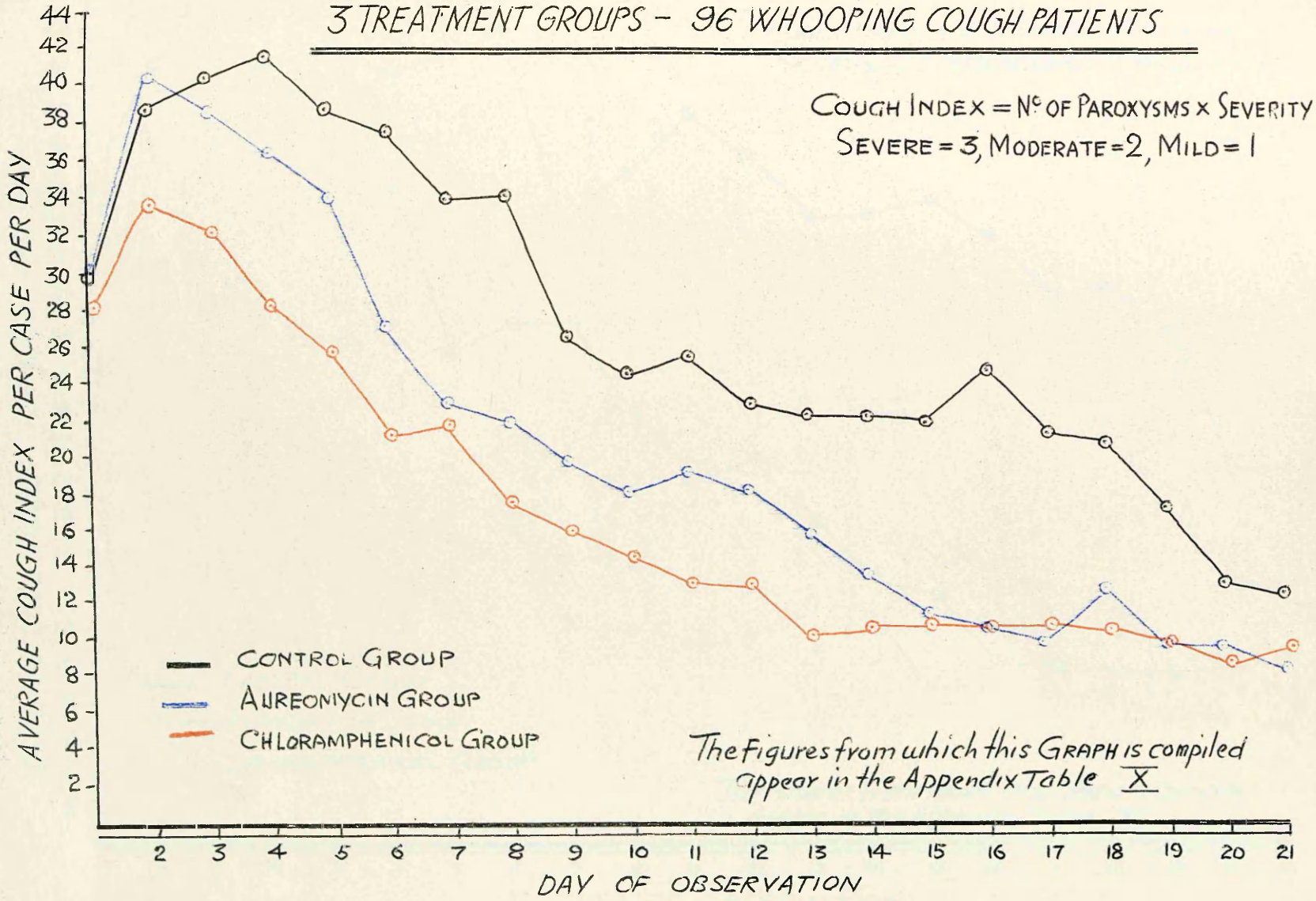
The resulting figure was termed the "cough index". The graphs of the average daily cough indices for the three treatment groups are shown in Figures 17, 18, 19 and 20 for all cases, and early, intermediate and late cases respectively.

Figures 18 and 19 show that the cough indices for treated patients in the early and intermediate cases fell during the first eight days of observation. No corresponding fall occurred in the control patients. For early cases, on the 8th day the average cough indices were 28.0 for patients treated with aureomycin, 18.3 for patients treated with chloramphenicol, and 44.2 for the control patients. For intermediate cases on the 8th day the average cough indices were 18.5 for patients treated with aureomycin, 23.2 for patients treated with chloramphenicol, and 30.2 for the control patients. Using the cough index it did not appear that late cases were influenced by treatment, as is shown in Figure 20.

These figures suggest that using the device of the cough index it appeared that the antibiotic had a greater effect on the intermediate cases than was shown by the initial analysis of the number of daily paroxysms.

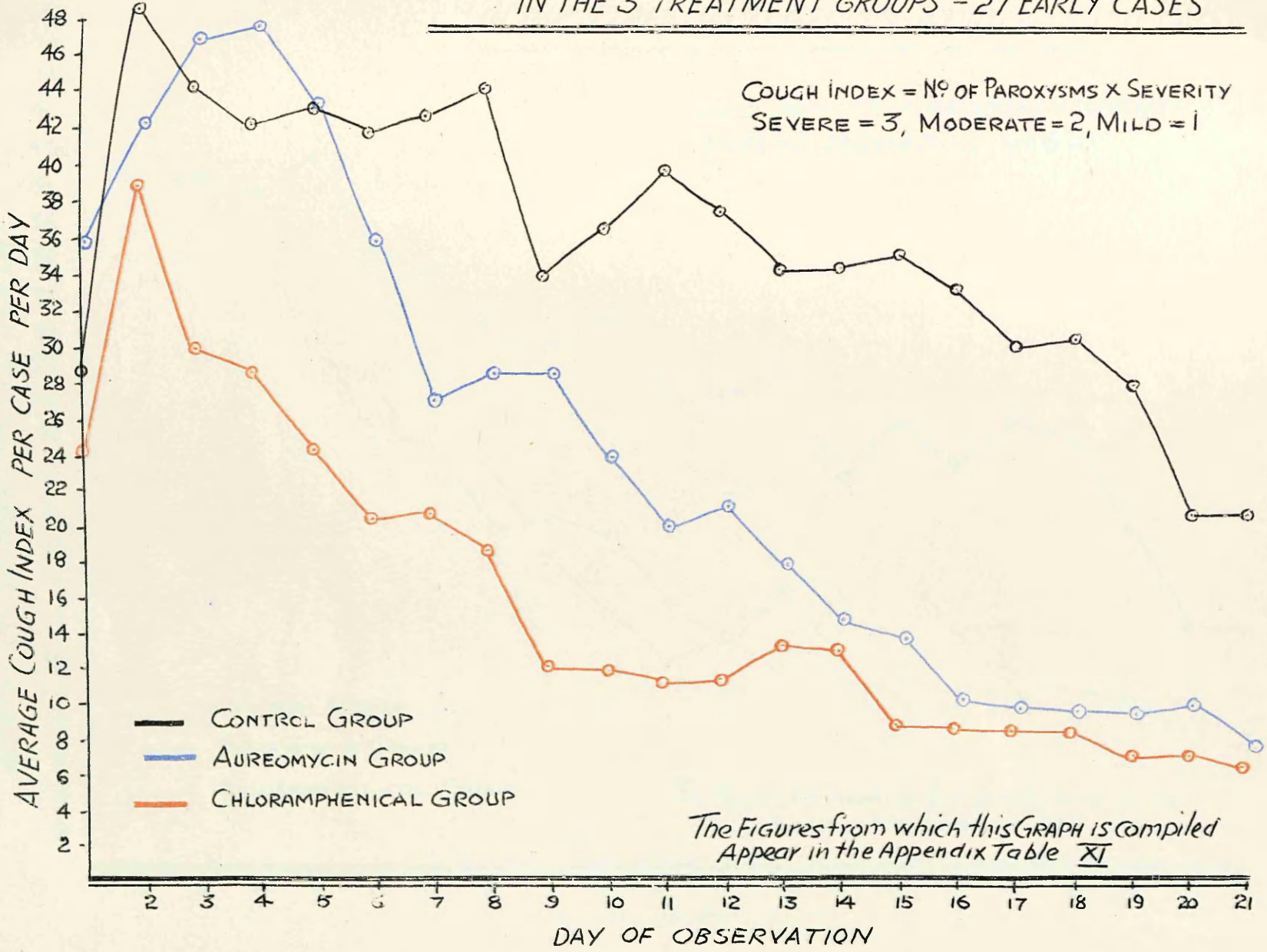
Chloramphenicol Relapse Cases. Relapse following the cessation of chloramphenicol treatment has been described by various authors (Payne et al., 1949, and Hazen et al., 1951). Of the 32 chloramphenicol treated cases in this series, five (15.6%) patients relapsed following the cessation of therapy. Of these five patients, four were early cases and one was an intermediate case. All were under 1½ years of age, and the relapse was diagnosed clinically before the treatment drug was known. The incident was characterized by a return of the rhinitis, an increase in the number and severity of paroxysms of coughing, and

FIG 17. THE AVERAGE COUGH INDEX PER CASE PER DAY IN THE 3 TREATMENT GROUPS – 96 WHOOPING COUGH PATIENTS



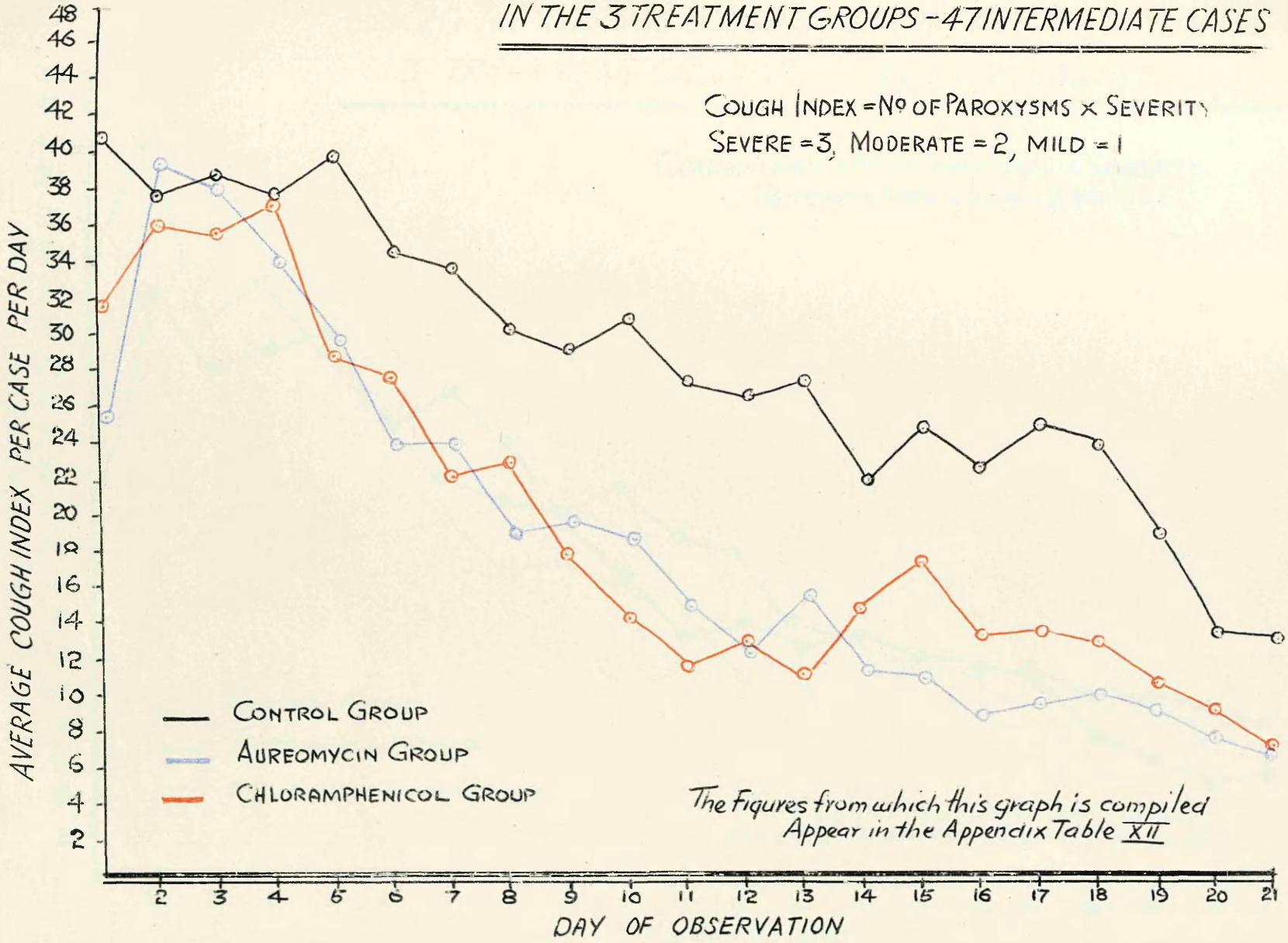
The Figures from which this GRAPH is compiled appear in the Appendix Table X

FIG 18. THE AVERAGE COUGH INDEX PER CASE PER DAY IN THE 3 TREATMENT GROUPS - 27 EARLY CASES



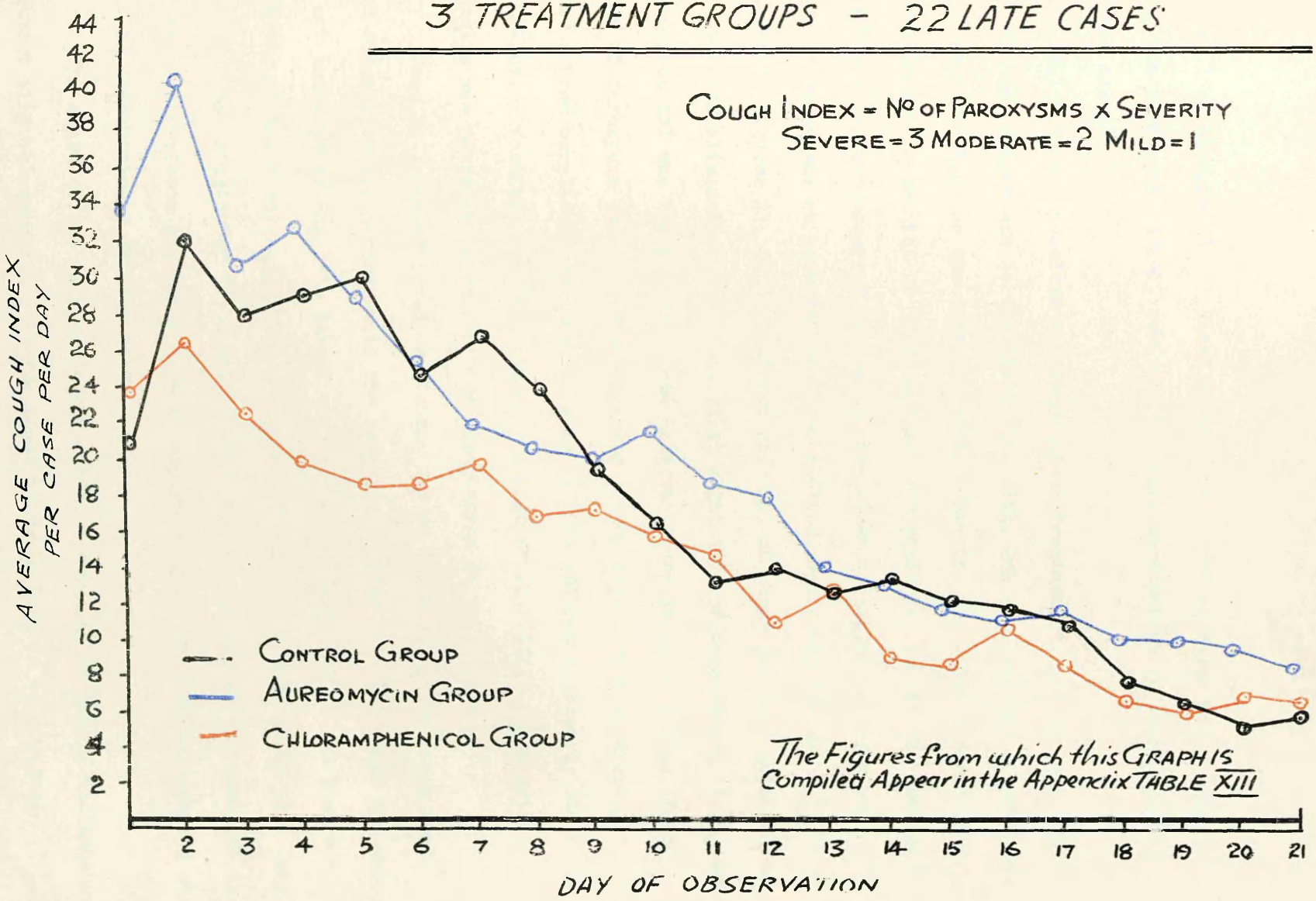
The Figures from which this GRAPH is compiled Appear in the Appendix Table XI

FIG. 19. THE AVERAGE COUGH INDEX PER CASE PER DAY IN THE 3 TREATMENT GROUPS - 47 INTERMEDIATE CASES



The Figures from which this graph is compiled Appear in the Appendix Table XII

FIG. 20. THE AVERAGE COUGH INDEX PER CASE PER DAY IN THE 3 TREATMENT GROUPS - 22 LATE CASES



The Figures from which this GRAPH IS Compiled Appear in the Appendix TABLE XIII

in some, loss of appetite. Chest signs of bronchitis, which had disappeared during the treatment period, returned and were accompanied by expectoration in three cases.

All patients received chloramphenicol treatment for seven days and the onset of the relapse was on the 11th, 9th, 11th, 8th and 15th day of observation, respectively, for the five patients. That is, the relapse occurred within four days of cessation of treatment in four patients, and in the remaining patient the relapse occurred on the 8th day after cessation of treatment. The number of paroxysms on each day has been plotted separately for each of the five patients in Figures 21, 22, 23, 24 and 25. All of these patients appeared to have improved clinically during the first eight days of observation (i.e., when chloramphenicol was being given), and this was accompanied by a fall in the number of paroxysms each day after the 2nd to 4th day. None of these patients suffered from complications, and the onset of the relapse is clearly shown on the graphs. Contrary to the findings of Hazen et al. (1951), Haemophilus pertussis was never isolated from the nasopharynx during a relapse.

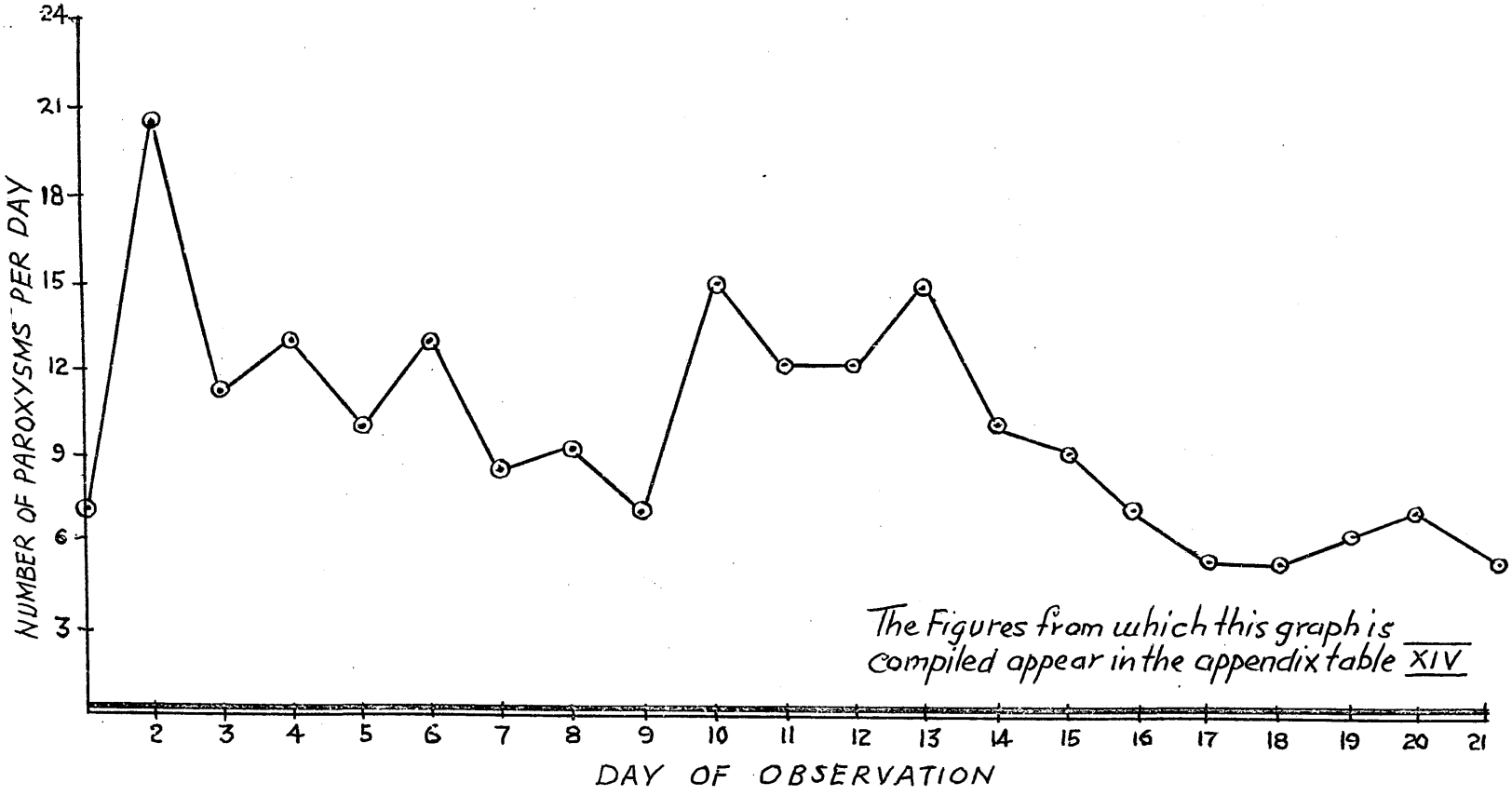
Case No.1 was admitted on the 2nd day of illness and the paroxysmal cough did not become severe until the relapse occurred. In this case the whoop was not heard until the 14th day of observation. Cases Nos. 1 and 5 were estimated as being severely ill; cases Nos. 2 and 3 were moderately ill; and case No. 4 was considered to be mild. Five to ten days after the onset of the relapse, the patients gradually made a good recovery. No similar relapses were noted in aureomycin or control cases.

The cause of the relapse is uncertain, but it may be due to the seven-day treatment with chloramphenicol being insufficiently long in some cases. I have

FIG. 21. CASE Nº 1 THE NUMBER OF PAROXYSMS per DAY IN A CASE OF WHOOPING COUGH TREATED WITH CHLORAMPHENICOL AND WHICH RELAPSED AFTER CESSATION OF TREATMENT

The figures from which this GRAPH IS compiled appear in the appendix table XIV

FIG 22. CASE Nº 2. THE NUMBER OF PAROXYSMS PER DAY IN A CASE OF WHOOPING COUGH TREATED WITH CHLORAMPHENICOL AND WHICH RELAPSED AFTER CESSATION OF TREATMENT



The Figures from which this graph is compiled appear in the appendix table XIV

FIG. 23 CASE 3 THE NUMBER OF PAROXYSMS PER DAY IN A CASE OF WHOOPING COUGH TREATED WITH CHLORAMPHENICOL AND WHICH RELAPSED AFTER CESSATION OF TREATMENT

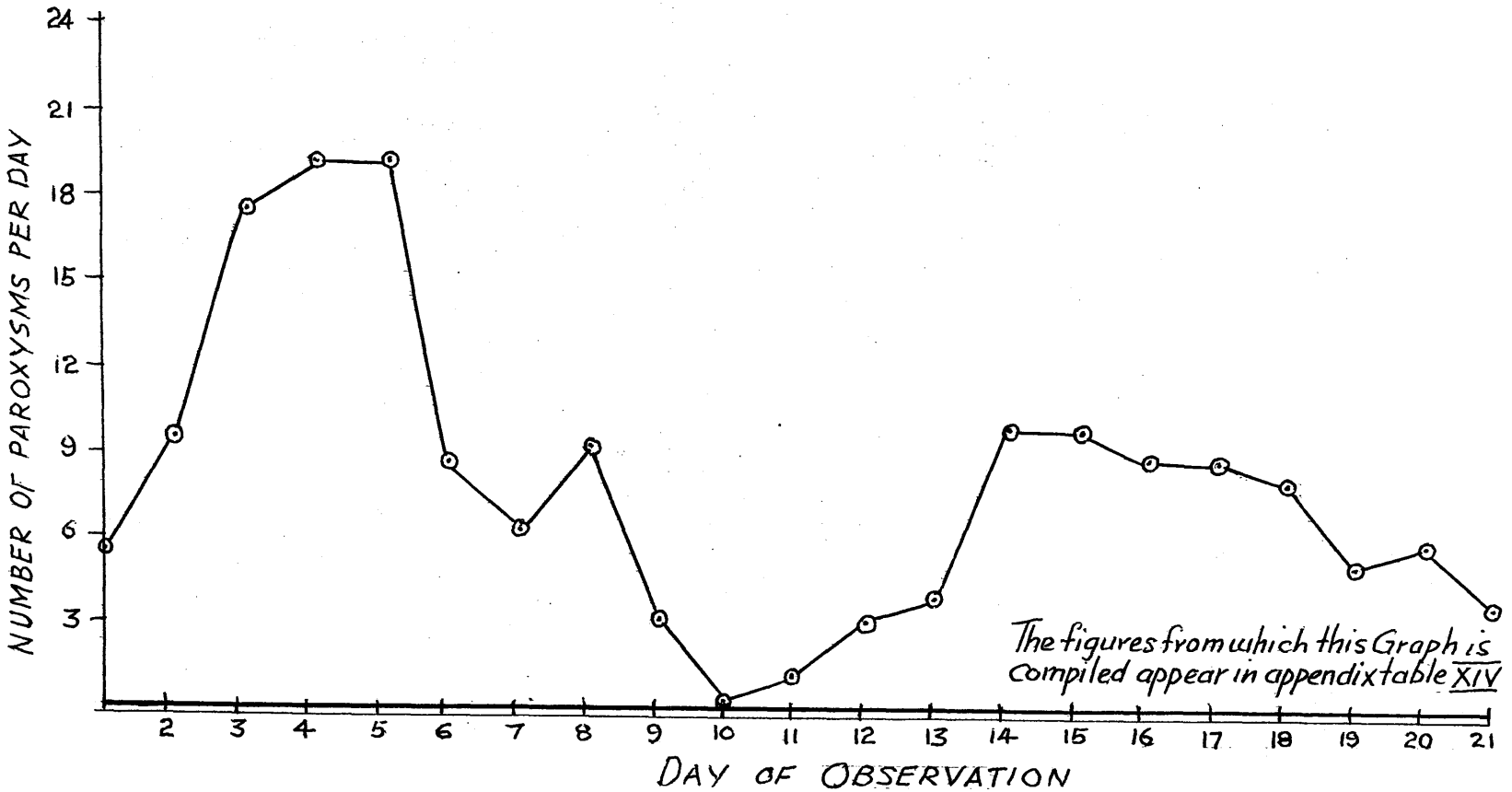


FIG. 24. CASE Nº4. THE NUMBER OF PAROXYSMS PER DAY IN A CASE OF WHOOPING-COUGH TREATED WITH CHLORAMPHENICOL AND WHICH RELAPSED AFTER CESSATION OF TREATMENT

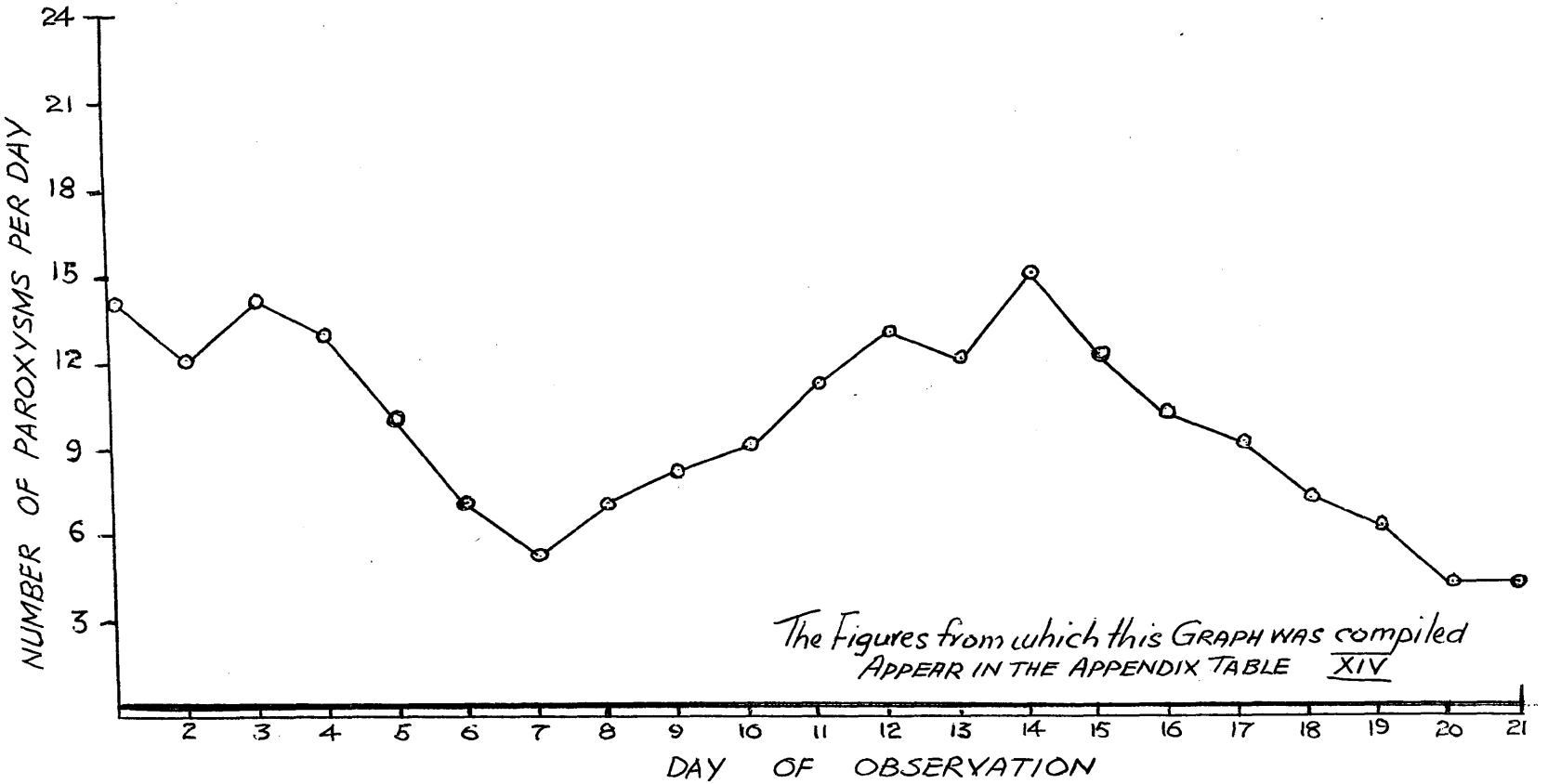
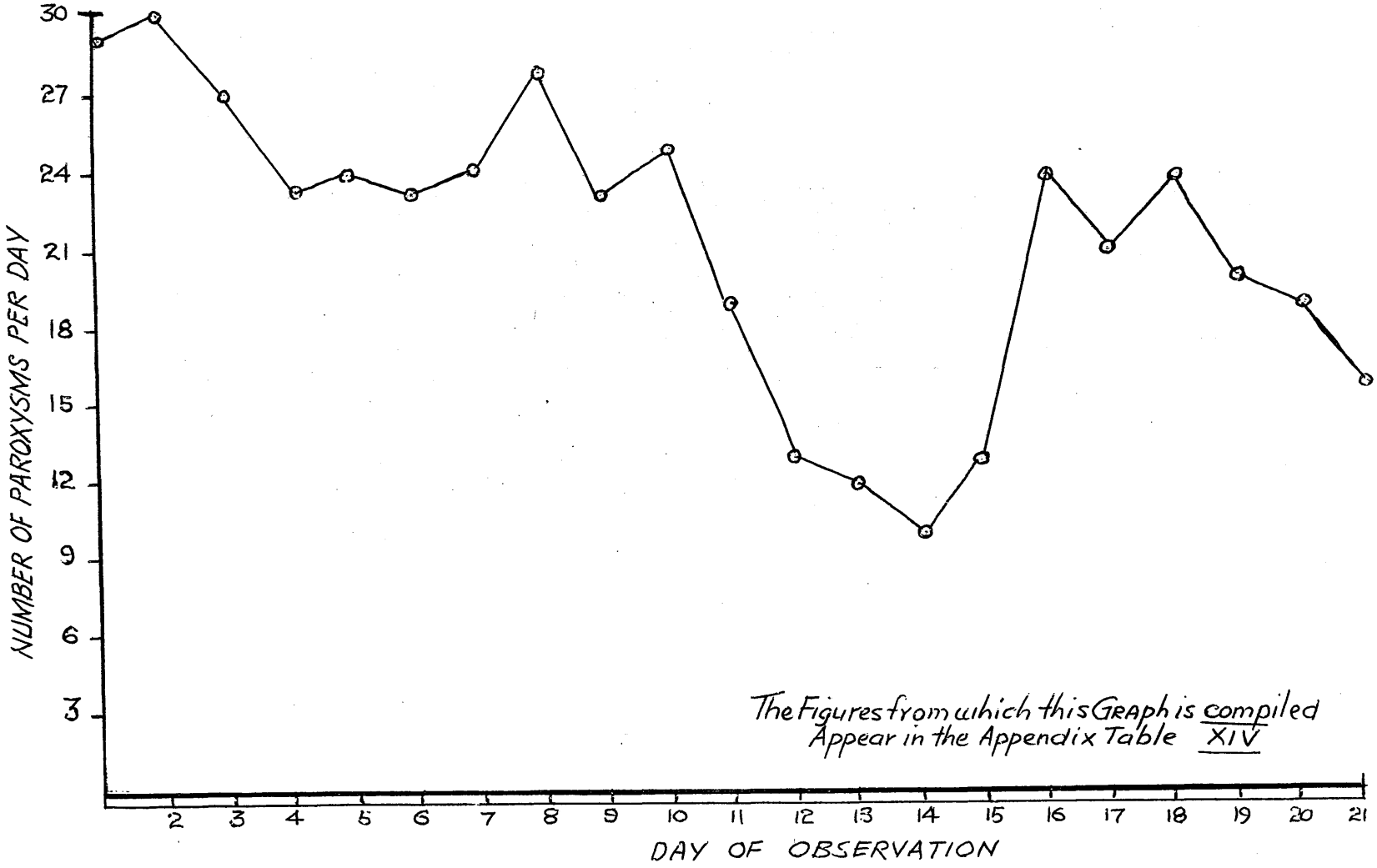


FIG. 25 CASE No. 5. THE NUMBER OF PAROXYSMS PER DAY IN A CASE OF WHOOPING COUGH TREATED WITH CHLORAMPHENICOL AND WHICH RELAPSED AFTER CESSATION OF TREATMENT



The Figures from which this Graph is compiled Appear in the Appendix Table XIV

since treated a further 17 whooping cough patients with chloramphenicol in the same doses for ten days and in no case did relapse occur. It may be that a standard seven-day treatment is not to be strictly adhered to.

Summary.

Analysis of the effect of aureomycin and chloramphenicol on the average number and severity of paroxysms indicated that from this aspect both drugs were equally effective in the treatment of whooping cough.

Aureomycin and chloramphenicol were effective in reducing the number of paroxysms provided treatment was started within the first eight days of illness.

Infants under one year of age responded more favourably to treatment than did children in the older age groups.

There was a strong indication that aureomycin and chloramphenicol were of value in reducing the number of paroxysms in severely ill patients, irrespective of the duration of the symptoms before treatment was commenced.

Five patients who received treatment with chloramphenicol relapsed after cessation of therapy

CHAPTER 9.

ON THE COMPLICATIONS OF WHOOPING COUGH WITH A NOTE ON THE TOXIC EFFECTS OF THE ANTIBIOTICS EMPLOYED IN TREATMENT.

For the purposes of this inquiry, a complication was defined as any infective condition associated with whooping cough which was considered to be severe enough to require immediate treatment with sulphonamides or antibiotics.

Of the 96 uncomplicated cases admitted to the series, 15 (15.8%) subsequently developed some complication, but only one of these developed a complication during the actual treatment period. Two of the 15 patients who developed complications died. Of the 15 complicated cases, seven were in the aureomycin treated group, six in the chloramphenicol group, and two in the control group (see Table 33).

When analysed by age and sex, no significant finding was discovered. On the whole, complications arose late in the illness. The average duration of illness prior to the onset of a complication was 26.7 days. On the average, children had been in hospital for 15 days before the onset of a complication. The illness was considered to be severe in ten of the 15 cases and moderate in the remaining five cases.

The following summarizes the nature of the complications:-

(a) Respiratory complications - 7 patients
(b) Otitis media - 5 patients
(c) Cachexia - 1 patient
(d) Convulsions and death - 2 patients

Respiratory Complications.

It is generally accepted that a mild degree of atelectasis is normal in whooping cough (Lees, 1950), although in most cases it is only diagnosed after X-ray examination. Atelectasis occurred in 31 patients and is fully described in another chapter. For the purpose of this chapter it is not discussed as a complication.

Table 33.

A Summary of Details concerning the 15 Whooping Cough Patients who developed Complications.

No.	Sex	Age Years	Treatment Group	Severity of Illness	Onset of Complication: Day of Illness	Onset of Complication: Day of Observation	Nature of Complication	Antibiotic Treatment of Complication	Response
1	F	$1\frac{5}{12}$	C.	Moderate	26	24	Tonsillitis & Otitis media	Penicillin	Good
2	F	$4\frac{1}{12}$	C.	Moderate	13	5	Broncho-pneumonia	Penicillin	Good
3	F	$1\frac{3}{12}$	A.	Severe	17	11	Bronchitis	Penicillin	Poor
4	M	$4\frac{10}{12}$	A.	Severe	16	9	Bronchitis	Penicillin, chloramphenicol	Poor Fair
5	M	$1\frac{9}{12}$	A.	Severe	23	10	Broncho-pneumonia	Penicillin	Good
6	M	$\frac{2}{12}$	A.	Severe	20	11	Atelectasis, Malnutrition	Penicillin	Nil
7	F	$3\frac{1}{12}$	A.	Severe	33	14	Bronchitis	Penicillin	Good
8	M	$\frac{7}{12}$	A.	Severe	26	14	Convulsions	-	Died
9	M	$\frac{9}{12}$	A.	Moderate	36	16	Otitis Media	Penicillin	Good
10	M	$\frac{6}{12}$	Ch.	Severe	25	18	Broncho-pneumonia	Sulphadiazine	Good
11	M	$\frac{8}{12}$	Ch.	Moderate	31	14	Otitis media	Penicillin	Good
12	M	$\frac{9}{12}$	Ch.	Severe	43	30	Otitis media	Penicillin	Good
13	F	4	Ch.	Severe	45	30	Bronchitis	Penicillin	Good
14	F	1	Ch.	Severe	22	9	Convulsions, Atelectasis	-	Died
15	F	$4\frac{4}{12}$	Ch.	Moderate	26	16	Otitis media	Penicillin	Good

C. - Control; A. - Aureomycin; Ch. - Chloramphenicol.

M - Male. F - Female.

Broncho-pneumonia developed during the course of the illness in three patients, one of whom was treated with aureomycin, one with chloramphenicol, and one control. The onset of the broncho-pneumonia was in the 5th day of observation in the control case, and on the 10th and 18th days of observation, respectively, in the aureomycin and chloramphenicol treated cases. In all three patients the onset was acute and the response to treatment by penicillin in two cases and sulphadiazine in one case was excellent. All three patients made an excellent recovery.

Bronchitis with a purulent sputum was noted in four patients, three who were on aureomycin and one who was on chloramphenicol. The onset was insidious and occurred after the cessation of treatment in all cases. Three of the patients were over $3\frac{1}{2}$ years of age and one patient was aged one year. Frequently the first signs noted were loss of appetite and a slight cough in between bouts of paroxysmal coughing. A mild pyrexia was present on occasions. Purulent expectoration was present and was frequently copious following paroxysms. Each patient was given intensive penicillin therapy, and in two cases the condition rapidly resolved. In the remaining two patients only slight improvement was noted. One patient received an additional course of chloramphenicol treatment but it was difficult to assess the part played by this in the ultimate recovery.

Otitis Media.

Otitis media was noted in five patients, of whom three were under one year of age and the remaining two under 18 months of age. In no case did this complication occur before the 14th day of observation, and, therefore, did not appear to be related to whether or not the patient had received antibiotic treatment. The onset was acute and responded dramatically to penicillin therapy. Otorrhoea did not occur in any of the patients. Haemolytic streptococci were

isolated from the throat in one case.

Cachexia.

A male child, aged two months, who was in the 8th day of illness, had typical signs of early whooping cough. He was admitted to the antibiotic trial and received treatment with aureomycin. During the 2nd week in hospital the child's condition deteriorated. He ceased to take his feeds and rapidly lost weight. He was pale, lethargic, cyanosed during paroxysms, and had a mild pyrexia. Radiological examination revealed extensive atelectasis at the base of both lungs. He became chronically marasmic and had to be tube-fed and nursed in an oxygen tent. During the following four weeks the child's general condition remained unchanged. Thereafter, slow improvement was noted and he was discharged from hospital 14 weeks after admission.

This case illustrates the extreme metabolic derangement that is occasionally a sequel to whooping cough. Skilled nursing is the only reliable treatment in such cases.

Convulsions and Death.

Of the 96 patients admitted to the trial, two developed convulsions and both were fatal.

Case No.1. A female child aged one year was admitted on 17th January, 1951. The patient came from a good home and there was no history of her having been in contact with another case of whooping cough. Paroxysmal cough with whoop had been present for 13 days before admission. Appetite had been poor but there was no history of vomiting.

On admission the child had puffy eyes and rhinitis. She was lethargic and exhausted after severe bouts of paroxysmal coughing with prolonged whooping.

There was a lot of tenacious mucous expectoration. The child appeared frightened and was severely ill. Examination of the chest revealed only signs of mild bronchitis. She was admitted to the antibiotic trial and received a 7-day course of treatment with chloramphenicol. Radiological examination of the chest on admission revealed a small patch of atelectasis at the left base.

During the first five days of observation she remained listless and difficult to feed. At no time did the temperature exceed 99°F. There were 9-11 paroxysms in each 24-hour period, and during each paroxysm the child whooped 30 times on an average. Some cyanosis was present during the paroxysms and she was exhausted afterwards. She had extreme difficulty in expectorating the thick tenacious mucus.

On the 9th day of observation (22nd day of illness), the patient became pale and collapsed. The respirations were shallow and the pulse almost imperceptible. Generalized convulsions began two-and-a-half hours before death. Treatment with phenobarbitone and coramine was unsuccessful.

Blood Counts:

18.1.51 Total leucocyte count - 80,000 per cubic millimetre.
Differential count -
Polymorphonuclear leucocytes ... 42%
Lymphocytes 57%
Monocytes 1%

23.1.51 Total leucocyte count - 62,000 per cubic millimetre.
Differential count -
Polymorphonuclear leucocytes ... 29%
Lymphocytes 65%
Monocytes 5%
Myelocytes 1%

Bacteriology: The result of pernasal swabs inoculated on Bordet-Gengou medium was as follows:-

17.1.51 - Pure growth of Haemophilus pertussis.
18.1.51 - Pure growth of Haemophilus pertussis.
19.1.51 - Pure growth of Haemophilus pertussis.
24.1.51 - No growth.

Permission to carry out a post-mortem examination was not granted.

This was an extremely severe case of whooping cough. At no time during the course of the illness did any improvement take place. Death occurred with the onset of convulsions.

Case No.2. A male child aged seven months was admitted on 19th February, 1951. The patient came from a good home where he had been in contact with a case of whooping cough who sickened six weeks previously. The child had developed coryza ten days before admission and paroxysmal cough three days before admission. There had been occasional vomiting.

On admission the child appeared pale and listless. Paroxysmal cough was heard and the child had profuse rhinitis. Examination of the chest revealed signs of bronchitis.

The child was admitted to the antibiotic trial and received a 7-day course of treatment with aureomycin. During that period the child had approximately 12 paroxysms in each 24-hour period.

The paroxysms were of moderate severity and did not cause much general upset. The temperature never exceeded 99°F. The patient made satisfactory progress as a result of treatment. Physical examination of the chest on the 8th day revealed no abnormality. Rhinitis was present and the child was feeding well.

Improvement continued until on the 14th day of observation (26th day of

illness) when he became unconscious. The pupils were small and reacted sluggishly to light. There was lateral nystagmus and bilateral internal strabismus which was greater on the right side than on the left. Deep reflexes were sluggish and superficial reflexes absent. Short generalized convulsions occurred. Lumbar puncture was performed and the cerebro-spinal fluid was normal. Sedation with phenobarbitone was of no avail. On the following day it appeared that there was slight improvement but convulsions again occurred and he died two hours later.

Blood Counts:

20.2.51 Total leucocyte count - 104,000 per cubic millimetre.
Differential count -

Polymorphonuclear leucocytes ...	40%
Lymphocytes	57%
Eosinophils	1%
Monocytes	1%
Myelocytes	1%

27.2.51 Total leucocyte count - 84,000 per cubic millimetre.
Differential count -

Polymorphonuclear leucocytes ...	20%
Lymphocytes	76%
Monocytes	4%

Bacteriology: The result of pernasal swabs inoculated on Bordet-Gengou medium was as follows:-

19.2.51 - Pure growth of Haemophilus pertussis.
20.2.51 - Pure growth of Haemophilus pertussis.
21.2.51 - No growth.
26.2.51 - No growth.
1.3.51 - No growth.

X-ray of Chest:

21.2.51 - There is a slight degree of collapse of the right middle lobe.
2.3.51 - No change.

Post-Mortem Report. Apart from a few haemorrhagic spots scattered over the pleural surfaces, the lungs appeared normal and well-aerated. No

abnormality was detected in the heart, pericardium, gastro-intestinal tract, or spleen. Apart from cloudy swelling, the liver was normal. There was no abnormality of the genito-urinary tract or the endocrine glands.

The meninges of the brain were normal. On section of the brain there was intense congestion of the grey matter in the anterior part of the left frontal lobe and posterior part of both occipital lobes. Elsewhere in the hemispheres the grey matter appeared normal.

The white matter, even in the affected areas, showed no naked eye changes. The cerebellum, pons and medulla were normal, and there was no evidence of cerebral haemorrhages.

Histology of the Brain: The haematoxylin and eosin sections of the affected part of the brain showed a moderate degree of diffuse softening with an increase of the leucocytes. There was marked congestion of the vessels, and a number showed fibrinous plugs with numerous polymorphs and leucocytes and also an attempt at early perivascular cuffing. Osmic acid sections showed no degeneration.

This was a severe case of whooping cough which appeared to be making good progress when convulsions developed which caused death. The histological report showed congestion of the cerebral vessels with minute haemorrhages and suggested early encephalitic changes.

Discussion.

In the series under consideration, 15.8 per cent of 96 whooping cough patients developed complications after admission. The complications tended to occur late in the illness. Treatment with aureomycin and chloramphenicol did not appear to reduce the incidence of complications as there were fewer cases

in the control group than in the treated groups. In none of the patients who received an antibiotic did a complication occur during the period when treatment was being given.

Broncho-pneumonia developed in three patients but all responded well to treatment. A type of persistent bronchitis with a purulent sputum has been described and this proved more difficult to treat than acute broncho-pneumonia. Otitis media was present in five cases, and it is probable that this was due to cross infection with Haemolytic streptococci. Smith (1927) isolated Haemophilus pertussis from the discharge in one case of otitis media. Infection of this type must be extremely rare and would be expected to occur early in the illness. Otitis media present only in the younger patients: whereas, bronchitis seemed to be the complication of the older age-groups.

Marasmus was a sequel in one infant. This complication was extremely refractory and pointed to the need for watchful and skilled nursing of whooping cough patients.

The two deaths were very distressing. Both patients received a full course of antibiotic therapy but despite this a fatal outcome was not prevented. Case No.1 showed no improvement at all during her stay in hospital. On the other hand, Case No.2 appeared to be making satisfactory progress before the onset of convulsions.

Toxic Effects of the Antibiotics employed.

The toxic effects which were observed as the result of treatment were as follows:-

	Aureomycin Group	Chloramphenicol Group	Control Group
Vomiting	7	3	0
Anorexia	2	3	0
Diarrhoea	0	0	0
Rashes	0	0	0
Blood Dyscrasia....	0	0	0

Toxic effects were not a problem. In no case were they serious, and in no case did treatment have to be stopped as a result.

Vomiting. While there was occasional vomiting following a single dose of the trial drug, vomiting was only considered as a toxic effect if it recurred after repeated doses. Frequently, the administration of the drug caused paroxysmal coughing followed by vomiting. In such cases a second dose was usually retained. Ten patients were recorded as having vomited following the second dose of the drug. When analysed by age, vomiting seemed to be more prevalent in the older age group. Aureomycin caused vomiting more frequently than did chloramphenicol.

Anorexia. Difficulty with feeding was noted only in infants. Frequently the feed following the administration of the drug was not taken; whereas the feeds in between the doses were taken reasonably well. In all cases the appetite returned to normal after cessation of the treatment.

Diarrhoea. In no case did diarrhoea occur as the result of antibiotic therapy.

Rashes. Close observation failed to reveal any drug rashes in the cases treated by antibiotics.

Blood Dyscrasia. At the time when this trial was being undertaken, Gill (1950), Rich et al. (1950), and Volini et al. (1950) had drawn attention to the possibility of haemolcgical complications of chloramphenicol treatment.

Serial blood examinations were carried out on all patients admitted to the trial. No evidence of blood changes which could be attributed to the antibiotics were discovered.

The only toxic effects encountered were vomiting and anorexia, and these were not difficult to overcome. Vomiting tended to occur in the older children and anorexia was confined to infants, but under skilled nursing they did not interfere with the conduct of the trial.

CHAPTER 10.

BACTERIOLOGICAL EXAMINATION OF THE PATIENTS UNDER TREATMENT.

Each patient admitted to the antibiotic trial was subjected to bacteriological examination on five occasions, namely, the 1st, 2nd, 3rd, 8th and 11th days of observation. The method employed was the pernasal swab, which has been described in a previous chapter. Immediately after being taken the swabs were inoculated on to Bordet-Gengou medium in Petri dishes. The plates were placed in sterile tins and incubated at 37°C. for 72 hours before the surface of the medium was carefully examined for colonies of Haemophilus pertussis. Thereafter, with daily examinations, incubation was continued for a further 72 hours or until the organism was isolated. Suspicious colonies were removed from the medium by a straight platimum wire and identified morphologically and by slide agglutination.

During the entire trial, I personally carried out all the bacteriological examinations. For the purpose of the trial, a positive swab was defined as one from which Haemophilus pertussis or Haemophilus parapertussis was isolated. Patients were referred to as being "swab-positive" if one of these organisms was isolated.

The Overall Results.

Of all 96 patients, 50 (52.1%) were swab-positive on at least one occasion, as is shown in Table 34. From these 50 patients Haemophilus pertussis was isolated in 49 cases and Haemophilus parapertussis in one case. When the results were analysed according to duration of illness prior to admission, it was discovered that positive swabs were present in 77.8 per cent of early cases, 46.9 per cent of intermediate cases, and 31.8 per cent of late cases. It is apparent, therefore, that the earlier the patient is examined bacteriologically the greater is the chance of isolating the causal organism.

Table 34.

Bacteriological Results - The Numbers with Percentages of Patients with Positive Swabs, divided according to Duration of Illness prior to Admission to Hospital.

Duration of Illness prior to Admission	Number of Patients	Number Positive	Percentage Positive
Early Cases	27	21	77.8
Intermediate Cases	47	22	46.9
Late Cases	22	7	31.8
All Cases	96	50	52.1

Over the five examinations, positive swabs were obtained in 41.9 per cent of control cases, 60.6 per cent of cases treated with aureomycin, and 53.1 per cent of cases treated with chloramphenicol, as is shown in Table 35. This apparent anomaly was due to random selection of cases in a restricted series.

Table 35.

Bacteriological Results - The Numbers with Percentages of Patients with Positive Swabs, divided according to Treatment Groups.

Treatment Groups	Number of Patients	Number Positive	Percentage Positive
Control Group	31	13	41.9
Aureomycin Group	33	20	60.6
Chloramphenicol Group	32	17	53.1
All Patients	96	50	52.1

Of 50 bacteriologically confirmed cases, only six patients had one positive swab on five examinations, 32 patients were swab-positive on two occasions, and 12 patients were swab-positive on three or more occasions, as is shown in Table 36.

Table 36.

The Number of Positive Swabs obtained in each of 50 Bacteriologically Confirmed Whooping Cough Patients.

Treatment Groups	One Swab Positive	Two Swabs Positive	Three or More Swabs Positive
Control Group	1	6	6
Aureomycin Group	3	14	3
Chloramphenicol Group	2	12	3
Total	6	32	12

When the day of observation on which the first positive swab was obtained in each case, it was discovered that 38 (76%) patients were positive on the first examination, i.e., on the day of admission. A further 11 (22%) patients were swab-positive for the first time on the 2nd day of observation, and only one (2%) was swab-positive for the first time on the 3rd day of observation, as is shown in Table 37.

Table 37.

The Day of Observation on which Positive Swabs were First obtained in 50 Bacteriologically Confirmed Whooping Cough Patients.

Day on which Positive Swab was first obtained	Patients Swab-Positive	
	No.	%
1st Day (Day of Admission)	38	76
2nd Day	11	22
3rd Day	1	2
Total	50	100

In this series, if only one swab had been taken from each patient, approximately a quarter of the swab-positive patients would not have been bacteriologically confirmed. It is, therefore, of value to take two pernasal swabs from patients when attempting to obtain bacteriological confirmation in whooping cough.

Table 38.

Bacteriological Results - The numbers with Percentages of Patients with Positive Swabs on the 1st, 2nd, 3rd, 8th and 11th Day of Observation - Divided according to Duration of Illness prior to Admission and Treatment Groups.

Intervals when Swabbed*	EARLY CASES						INTERMEDIATE CASES						LATE CASES						ALL CASES					
	Chloramphenicol Group		Control Group		Aureomycin Group		Chloramphenicol Group		Control Group		Aureomycin Group		Chloramphenicol Group		Control Group		Aureomycin Group		Chloramphenicol Group		Control Group		Aureomycin Group	
	Positive						Positive						Positive						Positive					
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I	6	66.6	4	44.4	4	44.4	6	66.6	4	28.6	7	43.8	1	16.7	3	37.5	3	37.5	13	40.6	11	35.5	14	42.4
II	7	77.8	6	66.7	7	77.8	7	77.8	4	28.6	9	56.3	1	16.7	2	25.0	2	25.0	15	46.9	12	38.7	18	54.5
III	4	44.8	3	33.3	4	44.4	3	33.3	2	14.3	3	18.6	0	0	1	12.5	1	12.5	7	21.9	6	19.4	8	24.2
IV	0	0	2	33.3	1	11.1	0	0	1	7.1	0	0	0	0	0	0	0	0	0	0	4	12.9	1	3.0
V	0	0	1	11.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3.2	0	0
Number of Patients Swabbed	9		9		9		17		14		16		6		8		8		32		31		33	

*I - 1st day of observation
II - 2nd ,, ,, ,,
III - 3rd ,, ,, ,,
IV - 8th ,, ,, ,,
V - 11th ,, ,, ,,

A detailed analysis of the number of swab-positive cases at the five intervals when swabbing was carried out for early, intermediate, and late cases, and for all cases is shown in Table 38. In all instances more positive swabs were obtained on the 1st day and on the 2nd day than on the 3rd day. Five cases, four of whom were early and one intermediate, were swab-positive on the 8th day, i.e., after the completion of the treatment period.

When analysing the effect of the antibiotics on the presence of Haemophilus pertussis in the nasopharynx, it was found that for all cases 12.9 per cent of control patients, 3.0 per cent of aureomycin patients, and no chloramphenicol patients remained swab-positive on the 8th day of observation. It is worth noting that a positive swab was obtained from one early control case on the 11th day. These findings are in keeping with the results of the Medical Research Council trial as a whole, and support the view by Gray (1950a) who was of the opinion that chloramphenicol speedily eradicated Haemophilus pertussis from the nasopharynx.

Contamination of the Plates with Secondary Invading Organisms.

As Haemophilus pertussis is a slow-growing organism, one of the main difficulties in its isolation was the presence on the Bordet-Gengou medium of secondary invaders which grow more quickly and tend to cover the entire surface of the medium. This difficulty was greatly reduced by incorporating penicillin in the medium. Despite this, on each occasion a proportion of plates were affected by penicillin insensitive flora. Careful note was kept of the type of organism, and the extent to which the surface of the medium was affected. For the purpose of the investigation the following three categories were used:-

(a) Slight contamination was said to be present when secondary invaders were present on less than 25 per cent of the surface of the medium.

(b) Moderate contamination was said to be present when secondary invaders were present on 25-75 per cent of the surface of the medium.

(c) Gross contamination was said to be present when secondary invaders were present on more than 75 per cent of the surface of the medium.

Generally speaking, it was not possible to isolate Haemophilus pertussis from grossly contaminated plates. In many instances, however, it was possible to isolate the organism when contamination was moderate. Slight contamination did not influence the growth of Haemophilus pertussis. Other haemophilic bacteria, which did not interfere with the growth of Haemophilus pertussis, were not considered to be contaminating organisms.

The number and extent of contaminated plates has been calculated separately for each 4-week period during which the trial was in progress. The percentage of contaminated plates and the percentage of positive plates was calculated, and the results are shown in Table 39. The percentage of contaminated plates varied from 10.1-23.1 per cent in four of the 4-week periods to 44.1 per cent on the 9th-12th weeks, and 52.0 per cent on the 17th-20th weeks. During these two periods the percentage of positive swabs fell to 4.9 per cent, whereas, during the other periods the percentage of positive swabs varied from 10.8 to 16.3 per cent. It would appear, therefore, that the number of positive swabs varied inversely according to the degree of contamination of the plates. During the two periods when a large number of plates were contaminated, a greater proportion of these were grossly contaminated than moderate and slight. In all other periods a lesser proportion of gross than moderate and slight contamination was noted.

Of the pernasal swabs taken on the 1st, 2nd and 3rd days of observation, 27 of the 288 plates which were inoculated were grossly contaminated.

Table 39.

The Number and Degree of Contamination of Bordet-Gengpu Plates Inoculated during the Antibiotic Trial Divided into 4-Week Periods

	Weeks 1-4	Weeks 5-8	Weeks 9-12	Weeks 13-16	Weeks 17-20	Weeks 21-24	Weeks 25-26
Total Number of Swabs taken in Each Period	148	227	202	198	204	74	39
Number of Contaminated Plates -							
Slight Contamination	11	17	10	9	30	8	3
Moderate Contamination	1	15	24	9	22	6	1
Gross Contamination	3	11	55	16	56	4	0
Total Number of Contaminated Plates*	15 (10.1)	43 (19.4)	89 (44.1)	34 (16.9)	108 (52.0)	18 (23.1)	4 (10.2)
Total Number of Positive Plates*	16 (10.8)	37 (16.3)	10 (4.9)	29 (14.6)	10 (4.9)	10 (13.5)	3 (7.7)

* The figures in parenthesis indicate percentages of the total number of swabs taken.

The organism responsible was Staphylococcus aureus in 14 instances, and anthracoid bacillus in four instances, as is shown in Table 40.

Table 40.

Organisms causing Gross Contamination of the Plates inoculated from the First Three Personal Swabs, showing the Number of Plates contaminated in each Instance.

Organism	1 Plate contaminated	2 Plates contaminated	3 Plates contaminated	Total
Staphylococcus Aureus	3	2	9	14
Anthracoid Bacilli	2	1	1	4
Yeasts	3	1	2	6
Other Organisms	3	0	0	3
All Organisms	11	4	12	27

Fungi were responsible in a further six instances, and other organisms, including Bacillus proteus, in three instances. When Staphylococcus aureus was present, the entire medium was altered and had a brown appearance with a strong acid smell.

In 12 of the 96 whooping cough cases, all three of the plates were grossly contaminated and thus it was impossible to isolate the causal organism from these children.

At all times, every possible care was taken to avoid contamination of the medium prior to and during inoculation by the pernasal swab. There appears to be little doubt that in some cases the secondary invading organism was present in the nasopharynx of the patient. During the 17th-20th week period when 52 per cent of plates were contaminated, structural alterations were being carried out in the laboratory, and it is thought this may have been responsible to a large

extent for this high incidence. On the other hand, no satisfactory explanation could be found for the high incidence of contamination during the 9th to 12th weeks.

Discussion.

I can find no instance of an author reporting that he was able to isolate Haemophilus pertussis from 100 per cent of a reasonably large series of whooping cough patients. This is contrary to what is experienced in other common infectious diseases, notably scarlet fever and diphtheria, when it is relatively easy to isolate the causal organism in the acute stage of the disease. In an attempt to discover the reason for this peculiarity in whooping cough, careful bacteriological control was carried out on all cases admitted to the antibiotic trial.

In the series, the causal organism was isolated from 50 (52.1%) of the 96 whooping cough patients. Positive swabs were obtained from 77.8 per cent. of early cases, 46.9 per cent of intermediate cases, and 31.8 per cent of late cases. The results were comparable with those of other workers, including Maclean (1937), Bradford et al. (1940), and Brooks et al. (1942), and were also considerably better than had been obtained previously in any of the Glasgow fever hospitals.

There is no doubt that Haemophilus pertussis was present in the nasopharynx more often in the late catarrhal and early paroxysmal stages than in the later stages of the illness. In the trial patients, the organism tended to disappear from the nasopharynx during the treatment period, and this was especially noticeable in the chloramphenicol-treated cases, none of whom had positive swabs on the 8th day of observation. Difficulty in isolating Haemophilus pertussis makes it advisable that more than one swab be taken from each case or suspected case when a bacteriological diagnosis is required.

The number of positive results in the series might have been higher had it not been for the overgrowth of penicillin insensitive flora on the Bordet-Gengou medium which made detection of Haemophilus pertussis impossible in 12 (12.5%) patients. There seems every reason to believe that in all early cases, the organism is present in the nasopharynx. Pernasal swabs appear to be the method of choice, and contamination with secondary invading organisms is appreciably less when this method is used than when postnasal swabs are used in the diagnosis of whooping cough (Cockburn and Holt, 1948). Batches of Bordet-Gengou medium appear to differ in their ability to support Haemophilus pertussis and this might be due to variation in the potatoes. To combat this difficulty, Lacey (1954) has produced a new medium for Haemophilus pertussis containing a diamidine (M. and B. 938), sodium fluoride and penicillin. This medium is highly selective for Haemophilus pertussis, and it is claimed that it is simple to prepare for routine use. In a strict comparison with Bordet-Gengou, the new medium yielded 28 per cent more positive cultures from pernasal swabs, and there was a reduced number of plates which were contaminated with secondary invaders. Whether or not this new medium will be of general value in the bacteriology of whooping cough remains to be seen. Personal experience, however, has led me to the belief that the isolation of Haemophilus pertussis is a highly skilled procedure, and that it is most satisfactory if the responsibility for all the bacteriological procedures involved rest with one person.

If antibiotic therapy is to be of value the earlier the diagnosis is made and treatment commenced the greater is the likelihood of the treatment being successful. Chloramphenicol and, to a lesser extent, aureomycin appear to eradicate the organism from the nasopharynx, but despite this the paroxysmal cough

and whoop continue. It must be presumed that early in the disease there is set in motion a powerful train of events which is at present not well understood and is difficult to interrupt by treatment.

C H A P T E R 11.

HAEMATOLOGICAL EXAMINATIONS AND RESULTS.

The total and differential leucocyte counts provide useful help in the diagnosis of whooping cough. Generally speaking, the total leucocyte count is normal in the early catarrhal stage, but is increased in the late catarrhal and paroxysmal stages (Gardner, 1936). In some cases there is a marked lymphocytosis, and a relative lymphocytosis is considered to be of diagnostic significance. Whitby and Britton (1950) state that a common reaction is an increase of the leucocytes to 15,000 to 20,000 per cubic millimetre. In the case of children under six months of age, however, the leucocyte count may be misleading. Lapin (1943) considered that if a child with a suspicious cough had a count of over 10,000 lymphocytes per cubic millimetre, there was a strong indication that the diagnosis was that of whooping cough.

During the antibiotic trial, total and differential leucocyte counts were carried out on all patients shortly after admission and at weekly intervals thereafter. The figures obtained were compared with the normal blood counts in childhood compiled by Still in 1927.

The Lymphocyte Count in the Diagnosis of Whooping Cough.

Total lymphocyte counts for each patient were compared with Still's table and the percentage increase was calculated. The results are shown in Table 41. It was considered that a 30 per cent increase in the lymphocyte count was of diagnostic significance. When all cases were considered it was discovered that there was no increase in the lymphocyte count in 20.8 per cent of patients, and an increase of less than 30 per cent in a further 12.6 per cent of patients. These findings are in keeping with those of Begg and Coveney (1935) who described the blood findings in 65 whooping cough patients,

and reported no increase in the lymphocyte count in 23 per cent of patients. An increase of 30-50 per cent was noted in 5.2 per cent of patients, an increase of 50-100 per cent in 20.8 per cent of patients, and an increase of over 100 per cent in 40.6 per cent of cases.

Table 41.

The Percentage Increase in the Lymphocyte Counts for 96 Whooping Cough Patients, divided according to the Estimated Severity of Illness.

Percentage Increase in Lymphocyte Count	Mild Cases		Moderate Cases		Severe Cases		All Patients	
	No.	%	No.	%	No.	%	No.	%
Nil	11	37.9	9	20.9	0	-	20	20.8
10 -	1	3.4	1	2.5	0	-	2	2.1
20 -	3	10.4	6	13.8	1	4.2	10	10.5
30 -	3	10.4	1	2.5	1	4.2	5	5.2
50 -	4	13.8	11	25.5	5	20.8	20	20.8
Over 100	7	24.1	15	34.8	17	70.8	39	40.6
Total	29	100	43	100	24	100	96	100

When the severity of the illness was considered in relation to the lymphocyte count, it was discovered that in severely ill patients some lymphocytosis was always present, and in the majority it was marked. The percentages of patients with more than 100 per cent increase in the lymphocyte count was 24.1 for mild cases, 34.8 for moderate cases, and 70.8 for severe cases, and, further, only 4.2 per cent of severe cases had a lymphocytosis of under 30 per cent, as is shown in Table 41. This finding is of considerable importance in that it gives an early indication of prognosis. During the trial some cases were admitted which were classified as moderate but a blood examination showed a considerable lymphocytosis. Within a few days most of these cases had to be classified as being severe. The results of the antibiotic

trial indicated that treatment with aureomycin and chloramphenicol was of more value in severely ill patients than in the moderate and mild cases (see Chapter 8). Lymphocyte counts should prove of value in these cases where difficulty is experienced in deciding whether to give or withhold antibiotic therapy.

Due to the difference in the duration of illness before admission, it was not possible to examine the blood in all cases during the 1st and 2nd weeks of illness, but an analysis of such cases as were available was made. Mean total leucocyte counts were calculated for each week of illness and compared. Further, the mean total polymorph and lymphocyte counts were calculated for each week of illness.

The mean total leucocyte count was 18.7 thousand per cubic millimetre during the 1st week, as is shown in Table 42. This figure indicated that in the average case the leucocytosis had been well established by the 1st week, i.e., during the late catarrhal stage. The highest mean total leucocyte count was found in the 2nd week when the figure was 20.8 thousand per cubic millimetre. Thereafter, a fall in the mean leucocyte count occurred, and by the 4th week the figure was down to 12.2 thousand per cubic millimetre.

On six occasions during the early stage of the disease, total leucocyte counts of over 40,000 per cubic millimetre were obtained. The highest total leucocyte count was 104,000 per cubic millimetre (polymorphonuclear leucocytes 40%, lymphocytes 57%). This count was obtained on the 11th day of illness in a male child aged seven months who was severely ill and died 16 days later.

Table 42.

Frequency Distribution of Total Leucocyte Counts in 96 Whooping Cough Patients, divided according to Week of Illness

Number of Cells per Cubic m.m. (in thousands)	Number of Patients					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
5	-	-	1	-	-	-
6	-	-	3	1	-	-
7	-	3	4	1	2	2
8	1	2	4	4	-	-
9	-	2	9	6	2	-
10	-	4	5	8	2	-
11	-	3	15	5	1	1
12	3	5	10	3	-	-
13	5	6	1	2	2	-
14	-	7	3	6	1	-
15	1	2	4	3	-	-
16	2	6	3	4	1	1
17	3	-	6	-	-	-
18	-	4	-	-	-	-
19	-	1	2	-	-	-
20	1	-	4	-	1	-
21	-	2	1	-	-	-
22	1	1	1	-	-	-
23	-	2	1	-	-	-
24	4	2	1	-	-	1
25	-	1	-	-	-	-
26	2	4	1	1	-	-
27	-	-	1	-	-	-
28	-	2	-	-	-	-
29	-	-	-	-	-	-
30	-	1	1	-	-	-
31	-	-	-	-	-	-
32	1	-	1	-	-	-
33	-	-	1	-	-	-
34	-	1	-	-	-	-
35	-	3	1	-	-	-
36	1	-	-	-	-	-
37	-	1	-	-	-	-
38	-	-	-	-	-	-
39	-	-	-	-	-	-
40	-	-	1	-	-	-
Over 40	-	3	2	1	-	-
Total	25	68	87	45	12	5
Mean Count in Thousand Cells per Cubic m.m.	18.7	20.8	15.8	13.4	12.2	13.2

Differential Leucocyte Counts and their Relation to the Treatment Drugs.

An analysis of the mean total lymphocyte count and the mean total polymorph count was made. This showed that the marked leucocytosis was mainly due to an increase in the lymphocytes. During the 1st week of illness, the mean total lymphocyte count was 14,156 per cubic millimetre, and the mean total polymorph count was 4,412 per cubic millimetre; during the 2nd week, the mean total lymphocyte count was 15,350 per cubic millimetre, and the mean polymorph count was 6,047 per cubic millimetre, as is shown in Table 43. The mean total lymphocyte count fell to 6,815 by the 4th week, while the mean total polymorph count remained relatively unchanged. At that time, the mean total leucocyte count and the mean total lymphocyte count were still raised.

The mean total leucocyte count and the mean total lymphocyte count remained elevated for six weeks in some cases, and were, in fact, still elevated at the time of discharge from hospital when clinical recovery seemed apparent. In three cases the leucocyte count had not returned to normal when the patients were re-examined three months later at a follow-up clinic.

For all cases, the average total leucocyte counts for cases in the 6th week of illness was 13,168 per cubic millimetre. This figure is somewhat higher than is generally stated, and is contrary to the findings of Sauer and Hambrecht (1929) that there was a leucopenia at the end of the disease.

Table 43.

Results of Total and Differential Leucocyte Counts in 96 Whooping Cough Patients divided according to the Week of Illness and Treatment Received. Average Numbers of Cells per Cubic Millimetre.

A - TOTAL LEUCOCYTE COUNT

Week	Control	Aureomycin	Chloramphenicol	All Cases
I	21,800	19,357	16,522	18,864
II	19,927	21,720	20,747	20,810
III	13,527	19,530	15,630	15,698
IV	12,160	15,760	12,348	13,415
V	12,000	11,166	14,700	12,208
VI	16,000	14,266	7,000	13,168
B - NEUTROPHIL POLYMORPHS				
I	4,760	4,611	3,822	4,412
II	4,425	5,327	6,339	6,047
III	3,750	4,336	5,153	4,450
IV	6,440	5,880	5,890	6,030
V	8,500	5,100	3,850	5,358
VI	7,800	9,400	3,400	7,880
C - LYMPHOCYTES				
I	14,925	14,155	11,822	14,156
II	14,580	16,060	11,700	15,350
III	8,500	16,160	9,400	10,850
IV	5,430	8,430	6,140	6,815
V	5,160	5,683	10,450	6,410
VI	8,000	4,667	3,200	5,080

Erythrocyte Sedimentation Rate.

As a diagnostic precedure, erythrocyte sedimentation rates were carried out whenever blood could be obtained from a vein in the anticubital fossa. In the younger patients this was not possible, and it was not considered justifiable to obtain venous blood by other means, such as from the femoral or jugular veins or the anterior fontanelle. Erythrocyte sedimentation rates were performed on 23 patients, using the Westergren method. Normal results were obtained in 22 patients. In a female child, aged three years, the readings were 12 millimetres after one hour, and 20 millimetres after two hours. These results are in keeping with those of Gold and Bell (1936) who discovered that the erythrocyte sedimentation rate is normal in whooping cough.

Summary.

It was considered that the lymphocyte count was significantly increased in 66.6 per cent of the 96 whooping cough patients.

The percentage of patients with more than 100 per cent increase in the lymphocyte count was 24.1 per cent for mild cases, 34.8 per cent for moderate cases, and 70.8 per cent for severe cases. It was considered that the lymphocyte count was helpful in prognosis, but absolute proof would only emerge with considerable experience.

The mean total leucocyte count was highest in the 2nd week of illness, and thereafter fell to normal during variable periods.

Treatment with aureomycin and chloramphenicol did not influence the total or differential leucocyte count.

C H A P T E R 12.

ATELECTASIS IN WHOOPING COUGH.

INCIDENCE AND COURSE WITH SPECIAL REFERENCE TO THE INFLUENCE OF THE ANTIBIOTICS USED.

Respiratory complications are an important factor in whooping cough, and because of this it was decided to carry out weekly radiological examinations on all patients admitted to the antibiotic trial. Broncho-pneumonia and atelectasis are the most common respiratory complications of whooping cough, and while broncho-pneumonia as a complication is the most fatal (Christie, 1945), the effect of atelectasis must not be underestimated. Lapin (1943) considered atelectasis to be a common occurrence especially in severely ill cases in infancy.

Broncho-pneumonia and a persistent bronchitis with purulent sputum complicated several cases in this series, and these conditions have been fully described in a previous chapter. The main purpose of this chapter is to discuss the incidence and influence of atelectasis in the series of 96 whooping cough patients examined, with the effect, if any, of the antibiotics in its prevention.

If a main bronchus is occluded due to extrinsic pressure, atelectasis of the part of the lung supplied by the bronchus will follow. Engel (1947) has stated that in whooping cough the hilar glands may be grossly enlarged, and, therefore, this mechanism could explain the frequent occurrence of atelectasis. However, in a series of 150 cases of whooping cough, in which atelectasis was noted in 43 per cent, Lees (1950) could find no evidence that the collapse was brought about in this way. It has been suggested that there is another mechanism by which atelectasis can be brought about. Lander and Davidson (1938) showed experimentally that the aspiration of viscid material into the peripheral parts of the bronchial tree may be followed by atelectasis due to blockage of the finer bronchi and bronchioles. Erwin (1939) considered that the tenacious

sputum in whooping cough produced atelectasis in this way, and Lees agreed with this view.

Whooping cough from which there is a slow recovery is said to be a precursor of bronchiectasis (Coope, 1948). The relationship of atelectasis to bronchiectasis has been pointed out by many workers including Ogilvie (1941) and Lander (1946). If broncho-pneumonia is the most common cause of mortality in whooping cough, then atelectasis with its risk of bromchiectasis may well be the most common cause of morbidity.

Methods of Examination for Atelectasis.

Complete collapse of the upper and lower lobes can often be detected clinically. Complete collapse of the right middle lobe, however, is difficult to detect in young children as the signs are frequently masked by compensatory emphysema. Lesser degrees of atelectasis due to occlusion of the terminal bronchioles, while most frequently encountered radiologically, varied greatly in their ease of clinical detection.

Pyrexia was absent in many patients with atelectasis and was never a reliable guide to this complication. Patients were seldom distressed and in few cases were the signs of broncho-pneumonia met with. The final diagnosis of atelectasis was, therefore, based on radiological examination.

Radiological examinations were carried out soon after admission and at weekly intervals thereafter. For routine examination, films were taken in the antero-posterior position, but when a lesion was detected or suspected, lateral or lordotic views were used to define the location. Lordotic views were found to be of great value in defining collapse of the right middle lobe.

In order to classify the degree of atelectasis in the affected lobes,

the collapse was described as being "slight", "moderate", or "marked". When the lobe was completely, or almost completely, collapsed, the condition was said to be "marked". Slight collapse implied a small patch of atelectasis in the lobe, while moderate collapse was a greater degree of atelectasis.

Atelectasis and Age-Group of the Patients.

Radiological evidence of atelectasis was discovered in 31 (32.3%) of the 96 whooping cough patients. When analysed by age-groups, atelectasis was met with in 36.8 per cent of patients in the age-group 3-5 years, 38.7 per cent of patients in the age-group 1-3 years, and 26.1 per cent in infants under one year of age, as is shown in Table 44. These findings are at variance with the opinion of Lapin (1943) who stated that atelectasis was more common under the age of one year.

Table 44.
Age Distribution of Atelectasis in 96 Whooping Cough Patients.

Age in Years	Number of Patients	Patients with Atelectasis	
		Number	Per cent
Under 1	46	12	26.1
1-3	31	12	38.7
3-5	19	7	36.8
Total	96	31	32.3

Lobar Incidence.

In some patients more than one lobe was involved, the lobes showing atelectasis at the same time or becoming affected at different stages of the illness. In all, 56 lobes were atelectatic in the 31 patients. In 13 (41.9%) patients, only one lobe was involved, in a further 12 (38.7%) patients, two lobes were involved, in five (16.1%) patients, three lobes were involved,

and in one (3.3%) patient, four lobes were involved, as is shown in Table 45.

Table 45.

Number of Lobes affected by Atelectasis in 31 Whooping Cough Patients.

Number of Lobes affected	Control Group	Aureomycin Group	Chloramphenicol Group	Total	Per cent
One	5	3	5	13	41.9
Two	4	3	5	12	38.7
Three ..	1	3	1	5	16.1
Four ...	-	1	-	1	3.3
Five ...	-	-	-	0	-
Total:	10	10	11	31	100

The lower lobes were involved in 75 per cent of instances, the right lower lobe being involved in 39.3 per cent of instances, and the left lower lobe in 35.7 per cent. of instances, as is shown in Table 46.

Table 46.

Lobar Distribution of Atelectasis in 31 Whooping Cough Patients, divided according to Treatment Groups.

Lobe	No. of Times involved			Total	
	Control Group	Aureomycin Group	Chloramphenicol Group	No.	Per cent
Right Lower	6	8	8	22	39.3
Left Lower	7	6	7	20	35.7
Right Middle	3	6	2	11	19.6
Left Upper	-	1	1	2	3.6
Right Upper	-	1	-	1	1.8
Lingula	-	-	-	0	-
Total:	16	22	18	56	100

The right middle lobe was involved in 19.6 per cent of instances, and in 5.4 per cent of instances the upper lobes were involved. Nicholson (1949)

reviewing a series of 39 whooping cough patients with atelectasis, discovered collapse in the right lower lobe in 89.6 per cent of cases, and in the left lower lobe in 48.2 per cent of cases. On the other hand, Lees (1950) in his series found that the left lower lobe was affected in 50.5 per cent of cases, and the right lower lobe was affected in 36.5 per cent of cases. Table 47 shows how often the lobes were affected singly and how often in combination.

Table 47

Anatomical Distribution of Atelectasis in 31 Whooping Cough Patients, divided according to Treatment Groups.

Lobe or Lobes	Control Group	Aureo-mycin Group	Chloram-phenicol Group	Total
Left Lower and Right Lower	3	2	4	9
Right Lower alone	2	2	2	6
Left Lower alone	2	0	2	4
Left Lower, Right Lower and Right Middle	1	3	0	4
Right Middle alone	1	1	1	3
Right Lower and Right Middle ...	1	1	0	2
Left Lower and Right Middle	0	0	1	1
Right Lung and Left Upper	0	1	0	1
Left Lower, Left Upper and Right Lower	0	0	1	1
Total	10	10	11	31

The Degree of Atelectasis and the Severity of Illness.

Of the 56 lobes affected, the atelectasis was judged to be slight in 41 (73.2%), moderate in 12 (21.4%), and marked in 3 (5.4%), as is shown in Table 48. Atelectasis was present in 3 (10.3%) patients, in whom the illness was mild, in 14 (32.6%) patients, in whom the illness was moderate, and in 14 (43.8%) patients, in whom the illness was severe. Atelectasis was, therefore, more frequently met with in severe cases than in moderate cases, and seldom met with in mild cases.

Table 48.

Degree of Atelectasis in 56 Lobes in 31 Whooping Cough Patients, divided according to the Severity of Illness of the Patients.

Degree of Atelectasis	Severity of Illness of Patients			Total	
	Mild	Moderate	Severe	No.	Per cent
Slight	2	18	21	41	73.2
Moderate ...	2	4	6	12	21.4
Marked	-	-	3	3	5.4
Total No. of Lobes affected:	4	22	30	56	100
No. of Patients affected:	3 *(10.3)	14 *(32.6)	14 *(43.8)	31	

* The figures in parenthesis indicate the percentage of the total numbers of patients who were affected by atelectasis.

Time of Onset of Atelectasis.

Collapse was noted in 56 lobes, and the week of onset in each instance is shown in Table 49. In 10 (17.9%) lobes the onset was in the 2nd week, in 10 (17.9%) lobes the onset was in the 3rd week, in 20 (35.5%) lobes the onset was in the 4th week, in 15 (26.9%) lobes the onset was in the 5th week, and in one (1.8%) lobe the onset was on the 6th week of illness. Atelectasis, therefore, developed most often during the 4th and 5th weeks of illness.

Table 49.

Week of Illness when Atelectasis was first noted in 56 Lobes in 31 Whooping Cough Patients, divided according to Treatment Groups.

Week of Illness	Control Group	Aureomycin Group	Chloramphenicol Group	Total	
				No.	Per cent
2	2	3	5	10	17.9
3	2	2	6	10	17.9
4	7	6	7	20	35.5
5	5	10	0	15	26.9
6	0	1	0	1	1.8
Total	16	22	18	56	100

Duration of Atelectasis.

In 36 (64.4%) lobes, re-expansion has occurred in two weeks, as is shown in Table 50. In a further five (9.0%) lobes, re-expansion had occurred by the 4th week. In four (7.0%) lobes, re-expansion took place within eight weeks, and in a further four (7.0%) lobes, re-expansion took place within three months. In two (3.6%) lobes, the collapse lasted for nearly four months, and in three (5.4%) lobes, the collapse was still present after four months. In cases where the general condition was such as to render them fit for discharge, this was not delayed because of radiological findings. Children who were discharged with positive radiological findings attended at a follow-up clinic. Three patients with persistent atelectasis are still under observation, and a description of these cases will be given later.

Table 50.

Duration of Atelectasis (in Weeks) in 56 Lobes in 31 Whooping Cough Patients, divided according to Treatment Groups.

Time in Weeks	Control Group	Aureomycin Group	Chloram-phenicol Group	Total	
				No.	Per cent
1	4	5	6	15	26.9
2	8	5	8	21	37.5
3	0	2	0	2	3.6
4	3	0	0	3	5.4
5-8	0	4	0	4	7.0
9-12	1	3	0	4	7.0
13-16	0	0	2	2	3.6
Over 16	0	2	1	3	5.4
Died	0	1	1	2	3.6
Total	16	22	18	56	100

Atelectasis and the Effect of the Antibiotics.

When the incidence of atelectasis was considered in relation to the three treatment groups, it was discovered that treatment with aureomycin and

chloramphenicol did not prevent atelectasis. Furthermore, atelectasis appeared at the same time of illness and lasted as long in patients who received antibiotic treatment as it did in control patients.

Atelectasis was present in ten patients in the control group, ten patients in the aureomycin group and 11 patients in the chloramphenicol group, as is shown in Table 45. The lobar distribution was comparable in patients in each of the treatment groups, as is shown in Tables 46 and 47. In some cases, atelectasis was noticed for the first time during the treatment period or after the course of treatment had been given. This indicates that the antibiotics did not prevent the occurrence of atelectasis. For example, among the aureomycin patients ten of the 22 affected lobes became atelectatic in the 5th week of illness. Furthermore, there was no reduction in the duration of atelectasis among the treated cases; in fact, the control group appeared to fare better. For example, after four weeks, only one lobe remained atelectatic in the control patients; whereas, ten lobes remained affected in the patients treated with aureomycin, and four lobes remained affected in patients treated with chloramphenicol, as is shown in Table 50.

The fact that chloramphenicol and aureomycin treatment has no effect on the occurrence of atelectasis in whooping cough patients is of considerable importance. In no instance can I find records of serial radiological examinations being carried out in a similar trial of antibiotics in the treatment of whooping cough. Other workers appear to have ignored atelectasis in evaluating the results of their clinical experience.

If, as Lees (1950) suggests, one of the causes of the initial collapse may be swelling of the bronchiolar mucosa, then one might expect this to be

infective in origin. As, in many cases, atelectasis occurs late in the illness, it would seem likely that secondary invading organisms rather than Haemophilus pertussis are responsible. However, atelectasis was seen to occur during or shortly after treatment with chloramphenicol and aureomycin, and thus it seems unlikely that the process is solely infective. It may well be that a toxin produced by Haemophilus pertussis causes damage to the bronchiolar mucosa at an early stage in the illness, and that in some cases the damage does not become apparent until later in the illness. This theory would explain why the antibiotics are not effective in preventing atelectasis.

Cases of Persistent Atelectasis.

In three patients atelectasis persisted for longer than 16 weeks. These cases are still under observation and a summary of the case records will now be given.

Case No. 1. A female child, aged 4 years, was admitted on the 14th day of illness. She was severely ill and had a well-developed paroxysmal cough and whoop with vomiting. At this stage she was apyrexial. Slight improvement was noted following the course of treatment with chloramphenicol, and the cough became loose and productive. On the 4th week of illness, the patient's condition deteriorated. She had a purulent sputum, and physical examination of the chest revealed râles at the left base with dullness on percussion. The temperature was intermittent to 99.8°F. A seven-day course of treatment with penicillin caused slight improvement, but it was not until the 8th week that the child's condition gradually improved. She was discharged on the 13th week of illness, by which time her general condition was good. Paroxysmal cough with whoop were still present.

On admission, radiological examination of the chest revealed collapse of the right middle lobe. By the 4th week of illness, the right middle lobe collapse had improved, and there was moderate collapse of the left lower lobe. On the 8th week, the radiological appearance was unchanged. By the 12th week, the moderate collapse of the left lower lobe was unchanged, but the right middle lobe had re-expanded. The radiological appearance remained unchanged for the following nine months.

Following discharge from hospital, the child continued to cough and had purulent sputum especially in the mornings. One year after her original illness she was re-admitted with acute left lobar pneumonia. On this occasion there was a rapid response to penicillin therapy, and on discharge from hospital, slight atelectasis at the left lower lobe was detected radiologically. Cough with a copious amount of purulent sputum was still present, and postural drainage was instituted. An attempt at bronchography was made under general anaesthesia but was unsuccessful. Despite this there is a strong indication on clinical grounds that this is a case of bronchiectasis.

Case No. 2. A male child, aged 1 year and 9 months, was admitted on the 13th day of illness. He was moderately ill, having a well-developed paroxysmal cough and whoop. He was apyrexial throughout the illness. Physical examination of the chest revealed harsh breath sounds and râles at both bases. No improvement was noted following the 7-day course of aureomycin.

On the 25th day of illness, the child developed broncho-pneumonia which resolved quickly when treated with penicillin. The child made a rapid recovery but physical examination of the chest revealed persistent râles at both bases. He was well when discharged after seven weeks in hospital.

On admission, radiological examination of the chest revealed slight atelectasis of the right lower lobe. On the 4th week of illness, slight atelectasis of the left lower lobe was noted, and the atelectasis of the right lower lobe had become marked. By the 6th week of illness, the left lower lobe had re-expanded, but the right lower lobe remained unchanged.

As this patient removed to another district, observation has not been carried out at regular intervals. He was last seen in July, 1954, when clinical examination of the chest revealed a few crepitations in the lower lobe of the left lung. Radiological examination showed inflammatory changes at both bases. During the past three years he has had a persistent cough and copious purulent sputum, especially in the mornings. He has suffered from repeated colds and attacks of "bronchitis", which were treated with sulphonamides by the general practitioner.

Clinically, this is a case of bronchiectasis, but as the child is attending another hospital with chronic supurative otitis media, and has enlarged tonsils and adenoids, bronchography will have to be postponed meantime.

Case No.3. A male child, aged two months, who was admitted on the 8th day of illness, had a paroxysmal cough but no whoop. He was well nourished and took his feeds well. Clinically, the chest signs were those of bronchitis. There was intermittent pyrexia to 99.8°F. during the first three days, but with aureomycin treatment the temperature returned to normal.

During the 3rd week of illness, the child's condition deteriorated. He was lethargic and suffered from loss of appetite. There was some cyanosis during paroxysmal coughing, and he was seriously ill. During the following three weeks he was placed in an oxygen tent from time to time. The temperature

was occasionally raised to 99°-100°F. General improvement was slow and the child was not discharged until the 13th week of illness.

Radiological examination of the chest on admission, i.e., during the 2nd week of illness, showed slight atelectasis of the right upper lobe and the right lower lobe. During the 3rd week, the right upper lobe had re-expanded, and there was no change in the appearance of the right lower lobe. There was also a degree of collapse of the right middle lobe. On the 4th week, the right upper and right middle lobes were unchanged, and, in addition, there was slight atelectasis of the left lower lobe. By the 5th week, the atelectasis of both lower lobes was moderate, and there was complete collapse of the right middle lobe. By the 8th week, there was only slight atelectasis in both lower lobes, and partial collapse of the right middle lobe. On the 12th week, the collapse of the right middle lobe was still present, although some re-expansion had taken place, otherwise the lung fields appeared clear.

Six months after the onset of the illness, re-expansion of the right middle lobe was complete, but slight atelectasis of both lower lobes had re-appeared. The child had a persistent cough with sputum and was susceptible to respiratory infections. Since that time he had been in hospital on four occasions with pneumonia.

This patient was last seen in May, 1954, when physical examination of the chest revealed rhonchi at the right base and râles in the lateral aspect of the left base. Radiological examination showed inflammatory changes at the left base. Cough persists and he frequently vomits copious amounts of swallowed sputum, especially in the mornings. This is undoubtedly a case of bronchi-ectasis.

These three patients have a typical history of bronchiectasis, and this confirms the work of Lander (1946) and Lees (1950), who indicated that there was a close relationship between atelectasis and bronchiectasis. In this series, bronchiectasis, as a sequel to whooping cough, occurred in three (3.1%) of 96 patients, and it is worth noting that the condition arose despite the administration of chloramphenicol in case No.1, and aureomycin in cases Nos. 2 and 3. In view of the chronic indisposition that bronchiectasis causes, the incidence is obviously a serious one.

Summary.

Radiological evidence of atelectasis was noted in 32.3 per cent of 96 whooping cough patients. It was small in extent in 73.2 per cent of the affected lobes, and there was complete re-expansion in 64.2 per cent of the involved lobes within two weeks.

In this series it was noted that 75 per cent of the involved lobes were the lower lobes, and the greatest incidence of atelectasis was noted in children in the age-groups 1-5 years.

Treatment with aureomycin or chloramphenicol had no effect on the prevention, limitation in extent, or duration of atelectasis in this series.

In three instances, atelectasis lasted for longer than 16 weeks, and these patients now have the symptoms and clinical signs of bronchiectasis.

CHAPTER 13.

THE INVESTIGATION OF CONTACTS OF PATIENTS SUFFERING FROM WHOOPING COUGH BY ENQUIRY AND BACTERIOLOGICAL METHODS.

During the six-month period in which the antibiotic trial was being carried out it was decided to carry out bacteriological examinations on as many contacts of confirmed whooping cough patients as possible. This additional investigation was carried out in order to observe the spread of infection among contacts, to determine the incidence of secondary cases of whooping cough in closed communities, and to determine if healthy carriers of Haemophilus pertussis exist. It was decided, therefore, to examine:-

(a) The staff of the two whooping cough wards in the hospital when the antibiotic trial was being carried out.

(b) Family contacts of patients admitted to the antibiotic trial.

(c) It was further considered that outbreaks or potential outbreaks of whooping cough in children's residential homes would present a good field of study. Arrangements were made with the Glasgow Health and Welfare Department to notify me whenever an institutional case of whooping cough was suspected.

In this investigation serial pernasal swabs were taken from 45 members of the staff of the whooping cough wards. Eighty-seven family contacts were examined in their homes where pernasal swabs were taken. In addition, I was called to visit children in eight residential homes, and in four homes actual cases of whooping cough were discovered.

In Copenhagen, Kristensen (1933) reported on 15 years' experience as to the occurrence of Haemophilus pertussis. He examined cough plates, pharyngeal and laryngeal cultures from 500 healthy persons who had not been in contact with whooping cough, and 301 persons who lived in close contact with a case of whooping cough for more than one week. He similarly examined 202

patients who were suffering from various diseases of the respiratory tract, other than whooping cough. Negative results were obtained from all except nine of the 301 contacts, all of whom later developed whooping cough. He found no healthy carriers of Haemophilus pertussis, although abortive and atypical cases were frequently found especially in adults. Blatt and Levin (1933), studying epidemics of whooping cough in three Chicago hospitals, reported having isolated Haemophilus pertussis from the nasopharynx of three patients who had had whooping cough and who did not later develop the disease.

The Staff of the Whooping Cough Wards.

Every two to three weeks during the period of the antibiotic trial, pernasal swabs were taken from the members of the staff of the whooping cough wards. The staff co-operated well, with the exception of two ward-maids who refused to have the examinations carried out. Swabbing was carried out on eight occasions, but changes in staff caused variation in the number of times each person was swabbed. A total of 195 swabs were taken from 45 apparently healthy persons in close contact with whooping cough, thirteen members of the staff being swabbed on seven or eight occasions, as is shown in Table 51. In no case was Haemophilus pertussis or Haemophilus parapertussis isolated from the nasopharynx in any of these contacts.

A careful note was made of the previous history of having had whooping cough in each case. Of the 45 persons swabbed, 26 gave a history of having had whooping cough, nine had no history of having had whooping cough, and in ten members of the staff, no accurate history of previous infection was obtained, as is shown in Table 52.

Table 51

Staff Contacts from whom Pernasal Swabs were taken, showing the Total Number of Swabs taken in each instance.

Number of Swabs	Number of Members of Staff swabbed	Total Number of Swabs taken
1	2	2
2	11	22
3	9	27
4	5	20
5	3	15
6	2	12
7	7	49
8	6	48
Total	45	195

Table 52

Staff Contacts from whom Pernasal Swabs were taken, indicating whether or not each Member had or had not previously suffered from Whooping Cough.

Members of Staff	Previous History of Whooping Cough			Total
	Yes	No	Don't Know	
Medical Officer ...	1	0	0	1
Sisters	0	2	0	2
Staff-Nurses	1	1	0	2
Nurses	23	4	8	35
Ward-Maids	1	2	2	5
Total	26	9	10	45

Head colds among the staff were frequent, and it was thought that they occurred more often when a new batch of patients in the catarrhal stage of the illness had been admitted. Previous experience of senior members of the staff suggested that they had fewer colds when working in a broncho-pneumonia ward. This observation was not controlled and bacteriology failed

to prove any association with Haemophilus pertussis.

Family Contacts.

Eighteen homes from which a case of whooping cough had arisen were visited, and all the families co-operated in permitting the taking of pernasal swabs from each member of the household. In all, 87 pernasal swabs were taken, and the number of members in the various households is shown in Table 53.

Table 53.

Family Contacts - showing the Number of Families Swabbed and the Number of Members in each Family.

Number of Members of the Family	Number of Families	Number of Swabs Taken
3	5	15
4	4	16
5	4	20
6	2	12
7	1	7
8	1	8
9	1	9
Total	18	87

Thirteen children had suffered from whooping cough within six weeks of swabbing and were convalescent at the time of the visit. One pernasal swab was taken from each member of the family at the time of the visit, and the family was later contacted to ensure that none of the members of the household had subsequently developed whooping cough. In no case was Haemophilus pertussis or Haemophilus parapertussis isolated.

Of the 87 contacts examined, only nine had no history of having had whooping cough, and in a further four, no accurate history was obtained, as is shown in Table 54. Of the 87 contacts, 43 were over ten years of age, and only three were under the age of one year. On three occasions, it was

discovered that older children in the family had recently suffered from whooping cough but that the general practitioner had not been called until the baby had taken ill. These children were usually treated by the grandmother, and this indicates the necessity for health education among certain sections of the population.

Table 54

Age Distribution of the 87 Family Contacts observed, showing the Previous History as to whether or not each Member had suffered from Whooping Cough.

Age	Previous History of Whooping Cough			Total
	Yes	No	Don't Know	
0-1 year	1	2	0	3
1-5 years	16	2	1	19
5-10 years	20	1	1	22
Over 10 years ...	37	4	2	43
All Ages	74	9	4	87

In the social classes involved, which were mostly IV and V, it was frequently possible to get an accurate previous history of infectious diseases from which each member of the family had suffered. On the other hand, in a large proportion of nurses, it was impossible to gain similar accurate histories.

Inquiry was made as to any other illness in the household in the six-week period prior to the visit. No significant illness was noted, although several of the adults reported having head-colds, the incidence did not appear unduly high.

Contacts in Children's Residential Homes.

The physician in charge of the children's homes informed me that actual or suspected cases of whooping cough had occurred during the 1950-51

epidemic. On four occasions, clinical and bacteriological examinations of the suspected case and contacts were negative, and, therefore, are not discussed in the description of institutional outbreaks. There were five actual outbreaks of whooping cough which occurred in four homes, in one of these two separate outbreaks occurred.

Soon after being notified I visited the home involved and took particulars as to degree of contact of the other children. Pernasal swabs were taken from all contacts at weekly intervals, and, when necessary, physical examinations were carried out. Children were divided into two categories: susceptible, if they had not previously suffered from whooping cough, and not susceptible, if there was a history of having suffered from the illness.

For convenience the homes have been referred to by initial letters, and a summary of each outbreak will be given.

Home A (1st Outbreak).

This home is run by the Children's Department of the Corporation of Glasgow for the long-term care of children up to the age of five years. About mid-December, 1950, a four-year-old female child, who had been admitted to the home two weeks previously, developed a severe head-cold and cough. At that time, whooping cough was not suspected, but later developments suggested that this was a "missed case" and the cause of the outbreak. About 3rd January, 1951, four children sickened with a similar illness, but it was not until 18th January, when three of the children developed a whoop, that the diagnosis was made. These three children were admitted to Ruchill Hospital that day and the fourth child, who developed a whoop four days later, was admitted to Knightswood Hospital. Clinically all these children had well-developed whooping cough, but bacteriological examination was negative for Haemophilus pertussis.

In the home, children were divided according to age into three units: under 1 year, 1-3 years, and over 3 years. There was free mixing between children in the two older age-groups, but the infants did not come into contact with the children over one year of age. There were 16 children in the home at the time of the visit, and the results of the weekly bacteriological examinations are shown in Table 55.

Table 55.

The Dates of Bacteriological Examinations in Home "A", showing the Number of Children examined on each occasion, Susceptibility to Infection, and the Number of Positive Swabs obtained.

Date	Total No. Swabbed	Total No. Susceptible	Total No. Not Susceptible	No. of Positive Swabs
23.1.51	16	14	2	4
29.1.51	10	8	2	1
5.2.51	9	9	-	0
13.2.51	9	9	-	0
19.2.51	8	8	-	0

Pernasal swabs were taken from 16 children, 14 of whom had not previously had whooping cough. As the result of the first visit, Haemophilus pertussis was isolated from four children, two of whom had been admitted to hospital before the bacteriological results were known. The remaining two patients were admitted following the result of bacteriological examination, and they did not develop signs of paroxysmal cough until the 3rd and 5th day of observation, respectively. A further case was diagnosed following the second visit, but thereafter no further positive cases were diagnosed.

In this outbreak all the affected children were in the age-group 1-5 years, and the infection was presumably from case to case. In this home there were 20 contacts of the original "missed case", and of these nine developed

whooping cough. Five cases were diagnosed bacteriologically.

Home B.

This home for unmarried mothers is run by the Salvation Army, and it is the custom for the mothers to remain in the home for a period of three months after the confinement until adoption of the children can be arranged. Fourteen infants, aged 2-4 months, and 12 unmarried mothers were in the home at the time when the outbreak took place. The mothers were in contact with each other and attended to their own children, who all slept in the same nursery.

One of the mothers absconded for a period of three weeks. When she returned to the home she had a severe head-cold and cough. It was a mild illness and of short duration. Cough, which was not paroxysmal, continued for ten days, but, as whooping cough was not suspected at the time, she mixed freely with the infants and attended to her own child. This girl had never had whooping cough and was not aware of having been in contact with a case during the period she was away from the home.

Seventeen days after the mother's return to the home, four children developed head-colds, and three days later a further two children sickened. In these cases, cough developed 5-8 days after sickening, but it was not until four days after the first children had sickened that a paroxysmal cough was heard in one case. The following day I visited the home and at that time the six children had well-developed clinical signs of whooping cough. Of the remaining infants, four had developed colds, and four were well.

Pernasal swabs were taken from the 14 infants and 12 mothers. Haemophilus pertussis was isolated from the four cases who had recently sickened, but not from the six children who had developed the illness 15 days

previously. All of these ten children were admitted to hospital and to the antibiotic trial. Pernasal swabs taken from the 12 mothers and four infants, who were well, were negative. The home was visited on three subsequent occasions, but no further sickness occurred and no positive swabs were obtained from any of the four infants nor from any of the mothers.

In this outbreak, 10 out of 14 children, all of whom were under the age of six months, developed whooping cough, and it must be presumed that the infection was introduced by an adult who had a sub-clinical attack of the illness. Four of the children were diagnosed bacteriologically before clinical signs of whooping cough had become apparent. No healthy carriers of Haemophilus pertussis were discovered.

Home C.

This home is run by the Children's Department of the Corporation of Glasgow for the long-term care of children aged 4-15 years. The children lead as normal a life as possible, attending school and mixing freely with each other and with the general public. At the time of the outbreak there were 29 children in the home.

A male child, aged 4 years and 10 months, who had resided in the home for three days, was admitted to Ruchill Hospital on 2nd March, 1951. He was moderately ill with whooping cough, and pernasal swabs were negative for Haemophilus pertussis. The dates of visits to the home and results of pernasal swabs taken are shown in Table 56.

Of the serial bacteriological examinations carried out, only one positive swab was obtained from a male child, aged five years, who developed a cold on 21st March, 1951, i.e., 19 days after the original whooping cough case had been admitted to hospital, as shown in Table 56.

Table 56.

The Dates of Bacteriological Examinations in Home "C", showing the Number of Children examined on each occasion, Susceptibility to Infection, and the Number of Positive Swabs obtained.

Date	Total No. Swabbed	Total No. Susceptible	Total No. Not Susceptible	No. of Positive Swabs
4.3.51	28	6	22	0
12.3.51	28	6	22	0
19.3.51	28	6	22	0
26.3.51	28	6	22	1
2.4.51	27	5	22	0
9.4.51	27	5	22	0

Following the isolation of Haemophilus pertussis from a swab taken on 26th March, the child was admitted to hospital. He was very well and the only sign was a slight cough which was not spasmadic. The cough continued for ten days, and the diagnosis of whooping cough was confirmed by two further positive swabs.

Of the 28 whooping cough contacts in Home C, only six had not previously suffered from the illness. One of these children developed a very mild illness which was only diagnosed as whooping cough following bacteriological examination. Prompt removal of this type of subclinical case might have been responsible for limiting the extent of infection in the home. No other illness occurred in the home during the period of observation.

Home D.

This home is run by the Corporation of Glasgow Health and Welfare Department for the short-term care of children under the age of five years, while their mothers are in maternity or other hospitals. A female child, aged two years, who was admitted on 1st March, 1951, developed a cold and slight

cough on 20th March. Eight days later, the cough became paroxysmal and the child was transferred to Belvidere Hospital where the diagnosis of whooping cough was confirmed.

There were 19 contacts, two of whom had previously suffered from whooping cough, and visits with bacteriological examinations were made, as is shown in Table 57.

Table 57.

The Dates of Bacteriological Examinations in Home "D", showing the Number of Children examined on each occasion, Susceptibility to Infection, and the Number of Positive Swabs obtained.

Date	Total No. Swabbed	Total No. Susceptible	Total No. Not Susceptible	No. of Positive Swabs
3.4.51	19	17	2	1
10.4.51	14	12	2	0
18.4.51	11	10	1	0
26.4.51	6	6	0	0

At the time of the first visit, a female child, aged three years, who had been isolated from the rest of the children, had early clinical signs suggestive of whooping cough. Pernasal swab was positive for Haemophilus pertussis, and this was the only secondary case which was bacteriologically proven.

Each week during which observation was being carried out, children were being discharged from the home. Two children who were discharged on 15th and 17th April, respectively, were admitted to Belvidere Hospital on 21st and 22nd April, respectively, with the diagnosis of whooping cough. A further three children, who were discharged on 9th, 12th and 18th April, respectively, sickened on 12th, 19th and 24th April with whooping cough and were treated at home. All other children remained well.

Of 19 whooping cough contacts in this home, six developed the illness. In only one case was a bacteriological diagnosis made.

Home A (2nd Outbreak).

A female child, aged ten months, was admitted to Home A on 18th March, 1951, and on 19th March, she developed bronchitis with a cough which became paroxysmal three days later when she was transferred to Ruchill Hospital, where the diagnosis of whooping cough was confirmed. Because the child had been living in a common lodging-house, she was kept in isolation and was never in contact with any of the other children in the home.

On the occasion of this outbreak, there were 21 other children in the home, but eight of these had suffered from whooping cough during the previous outbreak. Several pernasal swabs were taken and the results of these examinations are shown in Table 58. A male child, aged 11 months, was bacteriologically diagnosed as suffering from whooping cough, otherwise all children were well and pernasal swabs failed to reveal Haemophilus pertussis.

Table 58.

The Dates of Bacteriological Examinations in Home "A", showing the Number of Children examined on each occasion, Susceptibility to Infection, and the Number of Positive Swabs obtained.

Date	Total No. Swabbed	Total No. Susceptible	Total No. Not Susceptible	No. of Positive Swabs.
25.3.51	21	13	8	0
2.4.51	21	13	8	0
9.4.51	21	13	8	0
16.4.51	20	12	8	1
23.4.51	20	12	8	1
30.4.51	18	10	8	0
6.5.51	18	10	8	0
15.5.51	18	10	8	0
22.5.51	18	10	8	0

The one secondary case is of considerable interest as the presence of the organism in the nasopharynx was detected prior to the onset of clinical signs, and the duration of the incubation period was greater than one would expect. The child, who had been resident in the home for a period of seven months, was not in contact with the primary case. Weekly pernasal swabs were taken with negative results until four colonies of Haemophilus pertussis were isolated from a swab taken 24 days after the primary case had been removed to hospital. At this time the child was symptom-free and was isolated in the home. Thirty-one days after removal of the primary case the child was transferred to hospital. He had developed coryza and a slight cough, and three further pernasal swabs were taken, from which profuse growths of Haemophilus pertussis were obtained.

This patient was admitted to hospital on the 1st day of illness when he had slight cough, coryza, and signs of bronchitis on physical examination of the chest. From the 1st to the 8th day, treatment with chloramphenicol was given, and he appeared well after cessation of treatment. The cough had become paroxysmal on the 5th day and he commenced to whoop on the 11th day of illness. Three days after cessation of treatment his condition deteriorated and the paroxysmal cough became severe. Thereafter, the illness followed the expected course and the child made a good recovery.

The above patient became infected with Haemophilus pertussis without having been in contact with the primary case, and it must be presumed that the organism was carried on the person of one of the staff. In this case the incubation period appeared to be at least 31 days. Haemophilus pertussis was isolated from the nasopharynx during the incubation period and seven days

before the onset of the catarrhal stage. This finding is of considerable importance as the child was presumably infectious during the incubation period. Similar results were reported by Bogdan (1951) who isolated Haemophilus pertussis from the nasopharynx of four children four days before the onset of the catarrhal stage.

The numbers of contacts who developed whooping cough in the five outbreaks are shown in Table 59. In no case did the illness develop in a child in whom there was a previous history of having had whooping cough. 38.6 per cent of 70 susceptible contacts developed whooping cough.

Table 59.

Total Number of Contacts observed, indicating the Numbers in each Home who developed Whooping Cough and the History of their previously having had Whooping Cough.

Home	Susceptible Contacts			Non-Susceptible Contacts		
	Total	Developed Whooping Cough		Total	Developed Whooping Cough	
		No.	%		No.	%
A (1st Outbreak)	18	9	50.0	2	0	-
B	14	10	71.4	0	0	-
C	6	1	16.7	22	0	-
D	19	6	31.6	2	0	-
A (2nd Outbreak)	13	1	7.7	8	0	-
Total	70	27	38.6	34	0	-

Discussion.

A total of 195 pernasal swabs were taken from 45 members of the staff of the whooping cough wards, and 87 pernasal swabs from family contacts of whooping cough patients failed to produce Haemophilus pertussis. It seems probable, therefore, that the organism is not carried in the nasopharynx of healthy persons in close contact with the disease.

Observation was made of five institutional outbreaks in four separate homes which differed in many important respects. In Home A there were 18 susceptible contacts and nine (50%) of these developed whooping cough, five of whom were bacteriologically confirmed. All the affected children were aged 1-5 years and were in contact with each other, and there were no cases in infants under one year of age who were nursed separately from the older children. In the same home a second outbreak occurred in which a child who had not been in contact with the primary case developed whooping cough. Although, Haemophilus pertussis is not carried in the nasopharynx of healthy persons, it is feasible that the organism might be carried on the clothing of an adult attendant and so transferred from case to case.

Home C was for the care of similar children to Home A, but as the children were in an older age-group, there were fewer susceptible contacts. In this outbreak, one (16.7%) patient developed a very mild illness which would not have been diagnosed as whooping cough had bacteriological examination not been carried out. Ten (71.4%) out of 14 infants in Home B developed the illness, and in this outbreak an adult caused the infection. Undoubtedly, "missed cases" in adults and subclinical attacks in children play an important part in the spread of infection. Less satisfactory results were obtained from the follow-up of contacts in Home D due to the transitory character of the inmates. Six (31.6%) of 19 susceptible contacts developed the illness but only one of these was bacteriologically confirmed.

These findings confirm the work of Smith (1936) who observed that in a school of 600 boys, 130 of whom had not previously suffered from whooping cough, 26 secondary cases occurred.

The infectivity of whooping cough is lower than might be expected when compared with other common infectious diseases, such as chickenpox and measles. The most common mode of spread of the organism is by droplet infection although rarely infection may be carried by inanimate objects.

It is worth noting that in Home A a case of whooping cough was diagnosed bacteriologically seven days before the clinical onset of the disease. The fact that a child can carry Haemophilus pertussis in the nasopharynx for seven days before the onset of the illness is strongly indicative of the way whooping cough can be spread. The velue of early bacteriological examination is obvious as it allows early diagnosis to be made and isolation carried out. It is, therefore, important that in any suspected cases, especially in an institution, thorough bacteriological examination of the nasopharynx should be carried out in order that isolation be made as soon as possible. At the same time, a thorough bacteriological examination of the susceptible contacts is important as cases similar to the one described may well be detected and isolated before they can infect others. By these methods,outbreaks of whooping cough have been shown by experience to be quickly limited.

CHAPTER 14.

INFECTIONS WITH HAEMOPHILUS PARAPERTUSSIS.

The first indication that whooping cough could be caused by an organism other than Haemophilus pertussis was noted by Eldering and Kendrick (1937) and Bradford and Slavin (1937), who, working independently, described an organism isolated from whooping cough patients which was similar to Haemophilus pertussis but differed in certain morphological, cultural and serological respects. In the following year Eldering and Kendrick finally described in detail the organism which they called Haemophilus parapertussis. This organism which was similar to Haemophilus pertussis was considered to be a cause of whooping cough. In London, Donald (1938) on four occasions isolated from a series of whooping cough cases an organism which was similar to but differed in cultural characteristics from Haemophilus pertussis. His description of the colonies makesit clear that they were Haemophilus parapertussis although he did not recognise their significance at the time.

The bacteriology of Haemophilus parapertussis was first described in detail by Bruckner and Evans (1939). They compared the agglutination, complement fixation, and precipitation characteristics with those of Haemophilus pertussis. They drew attention to the close similarity to Haemophilus pertussis but indicated that the toxin produced by Haemophilus parapertussis was less potent than that of Haemophilus pertussis. A further full description of the bacteriological characteristics of Haemophilus parapertussis was given by Cruickshank and Knox (1946). Flosdorf et al. (1942) were of the opinion that the incidence of Haemophilus parapertussis infection in the community was widespread but that only relatively serious cases were diagnosed clinically.

Following on the preliminary clinical description by Eldering and Kendrick (1938), ten patients suffering from Haemophilus parapertussis infection were described by Miller et al. (1941), and only one of these patients presented the classical whooping cough picture. The remainder had only the signs of upper respiratory infection and bronchitis. It is worth noting, however, that two of these patients developed whooping cough due to Haemophilus pertussis within the next year. Cruickshank (1944) considered that infection with Haemophilus parapertussis did not afford protection against infection with Haemophilus pertussis. He also stated that, on the other hand, a Haemophilus pertussis vaccine would not protect against infection with Haemophilus parapertussis.

The first indication that Haemophilus parapertussis infection was not necessarily a mild disease was given by Zuelzer and Wheeler (1946) who described two fatal cases. Both these children died from pneumonia and convulsions. The clinical picture was similar to whooping cough and both patients had high lymphocyte counts. Nasopharyngeal swabs produced Haemophilus parapertussis on culture, and in one patient post-mortem cultures from the lungs were positive for Haemophilus parapertussis and negative for Haemophilus pertussis.

The Incidence of Haemophilus Parapertussis Infection.

Nowadays it is thought that approximately one per cent of all whooping cough cases are due to parapertussis infection (British Medical Journal, 1954; Vol. 1: p.532), but many infections with Haemophilus parapertussis may only be present as a mild coryza and bronchitis. In a small localised outbreak in Oxford in 1946, of 34 patients suffering from whooping cough, 11 were shown

to have been infected with Haemophilus parapertussis (Cruickshank and Knox, 1946). Lacey (1949) reported from London that he had isolated Haemophilus parapertussis from 14 out of 450 children with suspicious coughs. On the other hand, over a period of four years Banks (1951) did not isolate Haemophilus parapertussis from any of his whooping cough patients at the Park Hospital, London.

At the time of writing Haemophilus parapertussis had not been described in Scotland, and personal inquiry at the main infectious diseases hospitals in Glasgow and Edinburgh revealed that no case of infection with Haemophilus parapertussis has so far been recognised clinically or bacteriologically. During the course of the antibiotic trial three cases of infection with Haemophilus parapertussis were discovered, and one of these was in a patient who was suitable for inclusion in the trial. These three cases are the first to be described in Scotland.

Description of Three Cases of Haemophilus Parapertussis Infection.

As the illness is rare a full description of the cases will now be given. Follow up of contacts was carried out, and serial pernasal swabs were taken from all contacts.

Case No. 1.

A male child aged eight months was admitted with the diagnosis of "Bronchopneumonia" on 1st February, 1951. The patient came from a very dirty and overcrowded home. Cough had been present for a few weeks but became worse one week before admission. A seven-day course of sulphadiazine and penicillin had been given by the general practitioner. There was also a family history of tuberculosis.

Clinical Examination: The patient was pale and very cross. The temperature was intermittent to 101°F. and the pulse rate proportionately increased. Cough was present but not paroxysmal. There was no whoop. Examination of the chest revealed numerous moist sounds in all areas.

Blood Count:

2.2.51 Total leucocyte count - 11,800 per cubic millimetre.
Differential count -

Polymorphonuclear leucocytes ...	55%
Lymphocytes	35%
Eosinophils	2%
Monocytes	5%
Myelocytes	3%

Bacteriology: Pernasal swabs taken on 1st and 2nd February, 1951, and inoculated on Bordet-Gengou medium produced pure growth of Haemophilus parapertussis.

Radiological Examination of the Chest: Miliary tuberculosis was diagnosed on 2nd February, 1951. The child was transferred to an isolation ward and treated with streptomycin. Tuberculous meningitis developed later in the course of the illness, but in spite of this the patient made a good recovery.

Contacts of Case No. 1.

Family Contacts: The family lived in a one-apartment house in the densely populated Maryhill district of Glasgow. In addition to the patient, there were five adults and one male child aged five years living in the house. The boy aged five years was admitted to another hospital with the diagnosis "Bronchitis" on 21st January, 1951. Two of the adult members of the family developed head colds on 7th and 14th February, 1951, respectively. All members of the family gave a history of having had whooping cough previously.

Pernasal swabs were taken from each of them on three occasions, 7th, 14th and 21st February, 1951, with negative results.

Contacts in the District: Despite the rarity of parapertussis infection it was thought that other cases of whooping cough in the immediate neighbourhood might possibly have been caused by this organism. An attempt was made, therefore, to trace all cases of whooping cough from that neighbourhood who had been notified to the Public Health Department in the three months prior to the admission of case No. 1. There were 13 such cases, three of whom had been admitted to hospital. Pernasal swabbing of these cases did not reveal any parapertussis infection but one case was found to be positive for Haemophilus pertussis. There were no subsequent notifications in the neighbourhood in the following six weeks.

Patient Contacts in the Ward: There were 14 patients in contact with Case No. 1, and all these were suffering from bronchopneumonia or acute bronchitis. Serial pernasal swabs were taken at three-day intervals; the results are summarized below:-

Date	Number Swabbed	Number Positive	Number Negative
6.2.51	14	0	14
9.2.51	14	0	14
12.2.51	12	0	12
16.2.51	10	1	9
19.2.51	8	1	7
22.2.51	6	1	5
25.2.51	5	0	5
1.3.51	3	0	3
6.3.51	1	0	1

The contacts were isolated from newly admitted patients. When a contact had been discharged, visits were made to the patient at home. No patient developed any illness subsequent to discharge from hospital. One of the

contacts developed parapertussis and will be described as Case No. 2.

Staff Contacts: Pernasal swabs were taken from the sister, staff nurse, eight nurses and four ward maids on three occasions, 6th, 16th and 22nd February, 1951. No positive swabs were discovered. No illness was noted in any member of the staff.

Case No. 2.

A male child, aged five months, was admitted to the same ward as Case No. 1 on 1st February, 1951, with the diagnosis of "Bronchopneumonia". He was placed in the cot next to Case No. 1 who had not been diagnosed as suffering from parapertussis at the time. They were in contact for 36 hours.

The child had a cough and clinical examination of the chest revealed signs of acute bronchitis. The temperature was normal throughout the illness. Ten days later the child had improved considerably and the chest signs had returned to normal.

Blood Counts:

2.2.51 Total leucocyte count - 10,200 per cubic millimetre.
Differential count -
Polymorphonuclear leucocytes ... 32%
Lymphocytes 62%
Monocytes 4%
Myelocytes 2%

18.2.51 Total leucocyte count - 16,400 per cubic millimetre.
Differential count -
Polymorphonuclear leucocytes ... 6%
Lymphocytes 90%
Monocytes 4%

6.3.51 Total leucocyte count - 9,200 per cubic millimetre.
Differential count -
Polymorphonuclear leucocytes ... 25%
Lymphocytes 70%
Monocytes 3%
Myelocytes 2%

Bacteriology: The result of pernasal swabs inoculated on Bordet-Gengou medium was as follows:-

4.2.51 - No growth.
5.2.51 - No growth.
6.2.51 - No growth.
9.2.51 - No growth.
12.2.51 - No growth.
16.2.51 - Pure growth of Haemophilus parapertussis.
19.2.51 - Pure growth of Haemophilus parapertussis.
22.2.51 - Pure growth of Haemophilus parapertussis.
25.2.51 - No growth.
1.3.51 - No growth.
6.3.51 - No growth.

Radiological Examination of Chest: Slight atelectasis of the lower lobe of the right lung was noted on 16th February, 1951, and re-expansion occurred within 14 days.

On the 16th day after admission the child developed signs of bronchitis and rhinitis. While a cough was present it was not paroxysmal and no whoop was heard. Pernasal swabs at this stage became positive for Haemophilus parapertussis. This mild illness lasted for about five days, at the end of which time the patient appeared to have fully recovered.

Case No. 3.

A male child aged four years sickened on 20th April, 1951, when he developed rhinitis and a slight cough. The cough became paroxysmal and whooping commenced on 3rd May, 1951, and he was admitted to Ruchill Hospital on 10th May, 1951. The clinical picture was typical of a case of whooping cough, and on admission the patient was apyrexial. The child was admitted to the antibiotic trial and received a seven-day course of aureomycin. There was no improvement with treatment and the paroxysmal cough remained severe. Purulent sputum was noted following paroxysmal coughing, and this gradually increased after the cessation of aureomycin treatment. Chest

signs of bronchitis were present at the onset but diminished gradually during the treatment period. There were also signs of atelectasis at both bases.

Ten days after admission he became very restless and unwell. The temperature became elevated to 101°F, and a seven-day course of penicillin was given. This caused temporary improvement but five days after the cessation of penicillin treatment his condition again deteriorated. A seven-day course of chloramphenicol was then given with apparently good effect. He was discharged on 28th June 1951.

Blood Counts:

11.5.51 Total leucocyte count - 32,200 per cubic millimetre.
Differential count -
Polymorphonuclear leucocytes ... 44%
Lymphocytes 52%
Eosinophils 1%
Monocytes 3%

18.5.51 Total leucocyte count - 13,800 per cubic millimetre.
Differential count -
Polymorphonuclear leucocytes ... 47%
Lymphocytes 49%
Monocytes 3%
Myelocytes 1%

29.5.51 Total leucocyte count - 7,800 per cubic millimetre.
Differential count -
Polymorphonuclear leucocytes ... 52%
Lymphocytes 43%
Eosinophils 1%
Monocytes 4%

Radiological Examination of Chest: Radiological examination of the chest revealed moderate atelectasis of the lower lobe of the left lung, and slight atelectasis of the lower lobe of the right lung. Re-expansion of both of the involved lobes took place within the next four weeks.

Contacts of Case No. 3.

Family Contacts: The home contacts were two adults and one male child

aged seven years who lived in a two-apartment house in the Anderston district of Glasgow. All gave a history of having had whooping cough previously. The patient's father had a head cold and slight cough about 7th May, 1951, and his mother was in bed with a severe cold from 11th to 20th May, 1951. The mother had a degree of bronchitis and a cough which was not spasmodic. Pernasal swabs taken on 15th, 23rd and 28th May, 1951, were negative for Haemophilus pertussis and Haemophilus parapertussis.

Contacts in the District: In the immediate neighbourhood, eight whooping cough cases had been notified to the Public Health Department during the period from 20th March until 31st May, 1951. None of these was admitted to hospital. Pernasal swabs taken from all these children were negative for Haemophilus pertussis and Haemophilus parapertussis.

Patient Contacts in the Ward: Two patients were in contact with Case No. 3, and serial pernasal swabs taken at three-day intervals proved negative for Haemophilus parapertussis.

Staff Contacts: As Case No. 3 was in a whooping cough ward, serial pernasal swabs had been taken from all members of the staff. In no instance was Haemophilus parapertussis isolated.

The Bacteriology of Haemophilus Parapertussis.

It was noted that Haemophilus parapertussis grew more rapidly on Bordet-Gengou medium than did Haemophilus pertussis. The colonies of Haemophilus parapertussis appeared larger than these of Haemophilus pertussis after three days' incubation. Darkening of the medium around the colonies was noted, and in one instance there was primarily a dark olive green staining of the medium which occurred with all three strains after subculturing.

Morphologically the organisms were Gram-negative and indistinguishable in size and shape from Haemophilus pertussis. It was noted that when a colony of Haemophilus parapertussis was suspended in saline there was a tendency to clumping. This was especially noticeable when the slide agglutination test was carried out.

In all cases the slide agglutination test showed agglutination with the specific rabbit antisera to Haemophilus parapertussis and no agglutination to Haemophilus pertussis antisera. The plate with the first growth of Haemophilus parapertussis was sent to Professor Robert Cruickshank at the Wright-Fleming Institute, St. Mary's Hospital, London, who confirmed that culturally and serologically the culture was one of Haemophilus parapertussis, agglutinating to half-titre with the specific parapertussis antiserum and not at all with pertussis antiserum.

Discussion.

Three cases of infection with Haemophilus parapertussis in Glasgow have been described. Case No. 3 showed the typical picture of whooping cough in which there was persistent bronchitis with a purulent sputum. This child was severely ill and at one stage his condition caused some anxiety. Case No. 2 was very mild, and had bacteriological examination not been carried out it might have been missed. The manifestations of the infection were those of bronchitis and upper respiratory infection. It is interesting to note that this child had a raised leucocyte count with a relative and absolute lymphocytosis. In Case No. 1 the clinical picture was obscured by the child having tuberculosis. Both infections were present concurrently and were almost certainly not related.

The degree of infectivity was extremely low. Repeated bacteriological follow-up of contacts of Cases 1 and 3 revealed only one other case. Although

many of the contacts had "colds", repeated bacteriological examination in these cases revealed no evidence of Haemophilus parapertussis infection.

The incubation period of parapertussis has not previously been determined. Case No. 2 was in close contact with Case No. 1 for 36 hours and was negative bacteriologically shortly after admission and for the next 12 days. Sixteen days after admission the child developed a clinical illness accompanied by a positive pernasal swab for Haemophilus parapertussis. It was, therefore, concluded that the incubation period for parapertussis was 13 to 16 days. It was also noted that the organism was present in the nasopharynx for seven days. All three parapertussis cases were visited by me shortly before writing this thesis and in none was there a history of having subsequently developed pertussis or an illness similar to whooping cough. There have, however, been very few cases of whooping cough in Glasgow since 1951 and this may not be a very clear indication as to whether or not immunity to pertussis has been gained by the child having had parapertussis infection.

If we accept that infection with Haemophilus pertussis does not give protection against Haemophilus parapertussis then it would appear that inclusion of parapertussis antigen in whooping cough vaccines might become advisable. The scanty distribution of the infection would not justify such action meantime.

It is certain that improvement in the bacteriological diagnosis in whooping cough and an increase in the numbers of cases submitted for bacteriological proof would lead to a greater knowledge of parapertussis infection. It might well be that organisms other than Haemophilus pertussis and Haemophilus parapertussis play a part and may even be causes, in themselves, of whooping cough. This would explain the fact that in many cases of whooping cough no obvious causal organism can be isolated.

C H A P T E R 15.

GENERAL SUMMARY AND CONCLUSIONS.

Most of the infecticus diseases which formerly were responsible for many deaths in childhood have yielded to modern discoveries either in prophylaxis or therapy. Whooping cough alone, among the commoner infectious diseases, remains comparatively unchecked and is not infrequently fatal to infants who unfortunately are often the victims. Also, owing to its prolonged course the disease may cause much suffering in older children. For these reasons alone the need for an improved method of treating whooping cough has long been obvious, and with the advent of the more recent antibiotics it was natural to think that in them might lie the answer to the problem. To try to evaluate their value in the therapy of whooping cough a clinical trial was carried out using two of the more recent of the antibiotics, namely, aureomycin and chloramphenicol. The trial was conducted with great care and with modern refinements, including the precaution that observers of the patients under treatment were ignorant of which antibiotic was used in any individual case.

The effects of the two new antibiotics were assessed according to their influence on the following features of whooping cough: (a) the course of the illness, (b) the duration of hospitalization, (c) the number and severity of the paroxysms, (d) the number of complications, (e) the presence of Haemophilus pertussis in the nasopharynx, (f) the occurrence of atelectasis, and on (g) the blood leucocyte counts. The course and progress of the disease in the groups of patients treated with the two antibiotics were compared similarly with a group of patients receiving no antibiotic treatment.

It was found that while both aureomycin and chloramphenicol were of value neither proved more effective than the other, and neither one nor the other could be considered to be a highly effective remedy, and certainly not

to be considered of the same value as, for instance, the sulphonamides in the treatment of cerebro-spinal fever. Many patients appeared to benefit from treatment, and the duration of hospitalization was certainly less for those who received chloramphenicol therapy. However, although in a few cases dramatic improvement was brought about by treatment, in no case were the clinical signs of whooping cough completely suppressed. In a few cases relapse occurred after cessation of treatment with chloramphenicol.

The paroxysmal cough, which is the most prominent feature of the illness, was considered to be the most useful index to measure the effect of the antibiotics. It was found that patients treated within 8 days of the onset of the illness had a smaller average number of daily paroxysms than had those in the control group. Patients in whom treatment was commenced after the 8th day of illness were not affected in this respect by either aureomycin or chloramphenicol. The severity of the paroxysms was reduced by treatment in early cases, and to a lesser extent in those whose treatment was started later, but not at all in those whose treatment was not begun until the disease was well advanced. There was, however, a strong indication that treatment with aureomycin and chloramphenicol brought about a reduction in the number of paroxysms in infants under one year of age irrespective of the duration of illness prior to the commencement of treatment, and this is of considerable significance owing to the serious nature of the illness in the very young. It was also noted that severe cases in all age-groups responded more favourably to treatment than did moderately ill and mild cases. The favourable effect of the two antibiotics on the course of illness in the very young and in severely ill patients which was observed in this Glasgow

investigation was not indicated in the final analysis of the large clinical trial sponsored by the Medical Research Council.

Because of their bearing on treatment the value of certain procedures in early diagnosis was examined, and though the ideal proof undoubtedly lies in a positive bacteriology entailing the isolation of the causal organism, clinical examination and haematological examination are also valuable. While clinical signs and erythrocyte sedimentation rates were of suggestive though limited value, total and differential leucocyte counts were found to be of considerable help in diagnosis. In two-thirds of the patients the total lymphocyte counts were increased significantly. A high lymphocyte count was noted as being common in severe cases, and it became evident that more use of the blood examination might with advantage be made both as an index of prognosis and as a guide to the need for antibiotic therapy.

From over half the patients the causal organism, Haemophilus pertussis, was isolated, and the earlier in the illness that the bacteriological investigation was performed the greater was the likelihood of a positive result being obtained. The micro-organism was isolated from the nasopharynx during the catarrhal and early paroxysmal stage and was also shown to be present in the nasopharynx during the incubation period. This finding is regarded as of considerable importance not only in diagnosis but to implement the early isolation of cases in an effort to prevent the spread of infections in institutions. Owing to the unpredictability of the efficiency of Bordet-Gengou Medium, and the frequent overgrowth of the medium with penicillin insensitive flora, difficulty was often experienced in cultivating Haemophilus pertussis. Results obtained suggested that finality has not yet been reached in regard to the bacteriological

methods available for the diagnosis of whooping cough.

Bacteriological control of patients in the antibiotic trial showed that despite the fact that chloramphenicol, and to a lesser extent aureomycin, caused the organism to disappear from the nasopharynx there was not a comparable co-existing improvement in the clinical signs and symptoms of the disease. It was considered that early in the illness Haemophilus pertussis causes a sequence of events to be set in motion which are not much altered by treatment yet available. Further research into the pathogenesis of whooping cough is therefore required.

Perhaps the most disappointing aspect of the trial was that neither aureomycin nor chloramphenicol reduced the number of complications. Two patients who received antibiotic therapy developed convulsions and died. Bronchopneumonia and atelectasis developed in some cases despite therapy, and on occasions atelectasis was seen to arise during the period when treatment was being given.

While aureomycin and chloramphenicol do not present a complete answer to the problem of the effective treatment of whooping cough they appear to be the best weapons available at present. These antibiotics reduce the severity of the illness in early cases, in patients under one year of age, and in severely ill patients. Therefore, in view of the serious nature of the disease and the comparative absence of any significant toxic effects due to these substances it is recommended that aureomycin or chloramphenicol should be prescribed for all cases of whooping cough under one year of age, in all cases recognised within 8 days of the onset of the illness, and in all severely ill patients, until a more effective treatment, antibiotic or other, has been

introduced and subjected to a strictly controlled trial. The most satisfactory approach to the treatment of whooping cough lies not only in the search for an efficient drug but in the improvement of diagnostic methods so that early verification of the identity of the disease may be obtained. An extension of the use of pernasal swabbing would probably help to achieve this end.

Patients treated within 8 days of the onset of the illness respond favourably to treatment with aureomycin or chloramphenicol and early isolation limits spread of the infection.

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APPENDIX.

Table I

The Average Numbers of Paroxysms per Case per Day in the 3 Treatment Groups for 96 Whooping Cough Patients

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	12.6	1.0	13.6	0.9	12.7
2	15.0	3.3	18.3	2.0	16.3
3	14.4	1.6	16.0	0.3	15.7
4	13.0	2.7	15.7	0.5	15.2
5	11.9	3.4	15.3	0.4	14.9
6	10.1	2.9	13.0	0.7	12.3
7	10.9	3.6	14.5	3.6	10.9
8	9.2	3.8	13.0	1.8	11.2
9	8.8	2.1	10.9	0.4	11.3
10	8.5	2.7	11.2	0.5	10.7
11	7.8	4.4	12.2	2.8	9.4
12	8.5	2.8	11.3	1.6	9.7
13	7.9	2.7	10.6	2.4	8.2
14	7.5	3.0	10.5	1.7	8.8
15	8.9	2.3	11.2	4.4	6.8
16	6.8	5.2	12.0	5.0	7.0
17	7.5	3.5	11.0	4.3	6.7
18	7.1	3.4	10.5	3.8	6.7
19	7.2	2.1	9.3	2.6	6.7
20	6.9	1.3	8.2	2.2	6.0
21	6.1	1.6	7.7	2.0	5.7

Table II.

The Average Number of Paroxysms per Case per Day in the 3 Treatment Groups for 27 Early Cases

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	11.4	5.2	16.6	1.7	14.9
2	19.2	4.9	24.1	6.9	17.2
3	14.4	7.8	22.2	3.8	18.4
4	13.8	8.0	21.8	2.7	19.1
5	11.8	9.3	21.1	1.7	14.4
6	11.1	8.0	19.1	3.2	15.9
7	10,8	10.8	21.6	10.2	11.4
8	10.0	10.6	20.6	6.6	14.0
9	7.4	8.0	15.4	2.6	12.8
10	8.6	6.4	15.0	3.2	11.8
11	8.0	9.1	17.1	7.3	9.8
12	7.8	8.2	16.0	5.2	10.8
13	9.3	5.7	15.0	6.1	8.9
14	7.2	8.5	15.7	7.1	8.6
15	7.2	7.8	15.0	7.0	8.0
16	6.4	9.2	15.6	9.8	5.8
17	6.8	7.8	14.6	8.9	5.7
18	6.6	8.4	15.0	6.1	8.9
19	9.4	4.4	13.8	8.1	5.7
20	9.1	2.5	11.6	5.8	5.8
21	6.9	4.2	11.1	4.9	6.2

Table III.

The Average Number of Paroxysms per Case per Day in the 3 Treatment Groups for 47 Intermediate Cases

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	13.1	0.0	13.1	1.5	11.6
2	14.6	0.8	15.4	0.3	15.7
3	15.0	1.9	13.1	3.0	16.1
4	12.3	1.0	13.3	1.3	14.6
5	12.7	0.1	12.6	0.7	11.9
6	9.8	1.3	11.1	0.6	11.7
7	10.8	0.3	11.1	0.7	11.8
8	8.7	0.6	9.3	1.5	10.8
9	9.0	0.1	9.1	2.1	11.2
10	9.5	1.4	10.9	0.3	10.6
11	8.1	2.0	10.1	1.0	9.1
12	9.6	0.4	10.0	0.7	9.3
13	8.1	0.9	9.0	1.1	7.9
14	8.7	0.4	8.3	1.5	9.8
15	10.6	0.7	9.9	3.3	6.6
16	9.7	0.8	8.9	1.4	7.5
17	8.9	0.2	9.1	2.0	7.1
18	8.6	0.5	9.1	0.5	8.6
19	7.1	1.0	8.1	1.2	6.9
20.	6.9	0.8	6.1	0.2	5.9
21	5.6	1.1	6.7	1.2	5.5

Table IV.

The Average Numbers of Paroxysms per Case per Day in the 3 Treatment Groups for 22 Late Cases

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	13.2	1.1	12.1	1.0	13.1
2	10.0	7.9	17.9	1.5	16.4
3	12.5	1.5	14.0	2.4	11.6
4	14.0	0.7	13.3	1.0	12.3
5	10.2	3.4	13.4	1.2	14.6
6	9.5	2.3	11.8	1.8	10.0
7	11.2	1.2	12.4	3.8	8.6
8	9.3	2.0	11.3	2.4	8.9
9	10.2	1.2	9.0	0.8	9.8
10	7.5	0.0	7.5	2.5	10.0
11	6.7	3.4	10.1	0.6	9.5
12	6.5	1.8	8.3	1.0	9.3
13	5.6	2.8	8.4	0.8	7.6
14	4.8	3.7	8.5	1.5	7.8
15	6.8	2.1	8.9	3.3	5.6
16	3.5	10.0	13.5	7.4	6.1
17	5.2	5.2	10.4	4.1	6.3
18	3.8	3.7	7.5	1.4	6.1
19	4.0	2.4	6.4	0.1	6.5
20	3.9	3.1	7.0	1.2	5.8
21	3.7	0.8	4.5	0.0	4.5

Table V.

The Average Numbers of Paroxysms per Case per Day
in the 3 Treatment Groups
in 32 Moderately and Severely Ill Patients aged 0-1 Years

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	13.0	7.7	20.7	4.3	16.4
2	18.7	4.7	23.4	5.5	17.9
3	17.1	1.2	18.3	1.0	17.3
4	14.1	3.5	17.6	0.1	17.5
5	13.1	4.7	17.8	2.2	15.6
6	10.8	7.8	18.6	6.4	12.2
7	10.3	4.7	15.0	4.4	10.6
8	8.4	8.6	17.0	5.8	11.2
9	8.2	7.7	15.9	5.1	10.8
10	8.9	11.9	20.8	11.9	8.9
11	7.7	11.9	17.6	11.4	8.2
12	8.4	6.2	14.6	6.2	8.4
13	8.3	5.3	13.6	4.5	9.1
14	6.9	4.7	11.6	3.8	7.8
15	7.1	6.1	13.2	5.7	7.5
16	7.8	7.5	15.3	7.3	8.0
17	8.5	8.5	17.0	9.1	7.9
18	8.3	8.0	16.3	8.7	7.6
19	9.8	5.2	15.0	8.7	6.3
20	9.7	4.7	14.4	8.4	6.0
21	9.0	3.2	12.2	6.9	5.3

Table VI.

The Average Number of Paroxysms per Case per Day
in the 3 Treatment Groups
in 21 Moderately and Severely Ill Patients aged 1-3 Years

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	16.0	2.2	18.2	5.2	13.0
2	12.5	7.0	19.5	3.1	22.6
3	15.9	2.9	18.8	0.9	17.9
4	11.0	9.7	20.7	3.6	17.1
5	13.3	7.9	21.2	5.6	15.6
6	13.8	7.5	21.3	6.2	15.1
7	13.5	2.2	15.7	3.2	18.9
8	10.9	3.1	14.0	2.1	16.1
9	12.4	0.1	12.3	1.3	13.6
10	11.9	1.8	13.7	0.3	13.4
11	9.9	2.8	12.7	1.5	14.2
12	10.9	0.6	10.3	2.4	12.7
13	11.2	3.9	7.3	4.4	11.7
14	10.0	1.0	9.0	1.0	10.0
15	11.0	3.0	8.0	1.9	9.9
16	6.9	0.8	7.7	2.4	10.1
17	8.4	2.1	10.5	0.6	9.9
18	7.1	2.1	9.2	2.4	11.6
19	6.0	3.3	9.3	0.3	9.0
20	5.6	2.9	8.5	1.6	6.9
21	4.6	4.1	8.7	2.6	6.1

Table VII.

The Average Number of Paroxysms per Case per Day
in the 3 Treatment Groups
in 14 Moderately and Severely Ill Patients aged 3-5 Years

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	13.5	1.3	14.8	2.0	12.8
2	12.5	9.1	21.6	0.0	21.6
3	18.3	2.7	21.0	0.4	20.6
4	12.2	5.6	17.8	2.0	15.8
5	8.8	5.5	14.3	1.5	15.8
6	9.0	4.2	13.2	0.8	14.0
7	9.0	1.4	10.4	0.7	11.1
8	8.8	3.4	12.2	3.6	8.6
9	8.8	6.0	14.8	1.6	13.2
10	8.3	3.7	12.0	2.8	9.2
11	8.5	1.7	10.2	1.0	9.2
12	9.2	0.6	8.6	0.1	8.7
13	4.0	3.6	7.6	1.0	6.6
14	7.0	0.2	6.8	0.4	7.2
15	8.3	0.2	8.5	1.9	6.6
16	5.3	3.7	9.0	3.0	6.0
17	7.5	1.1	8.6	2.0	6.6
18	6.3	0.4	5.9	0.0	5.9
19	6.0	0.2	6.2	1.0	5.2
20	5.8	0.6	6.4	1.2	5.2
21	5.4	0.8	6.2	1.2	5.0

Table VIII.

The Average Numbers of Paroxysms per Case per Day in the 3 Treatment Groups in 12 Severe Cases Treated 1-10 Days from the Onset of the Illness

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	14.3	0.7	15.0	5.3	20.3
2	16.0	9.8	25.8	3.5	22.3
3	18.3	4.3	22.6	0.7	23.3
4	18.7	4.3	23.0	4.7	18.3
5	13.7	12.1	25.8	8.0	17.8
6	12.7	7.7	20.4	1.4	19.0
7	10.3	13.7	24.0	7.5	16.5
8	8.3	13.5	21.8	10.5	11.3
9	7.0	9.2	16.2	4.7	11.5
10	6.3	8.9	15.2	3.9	11.3
11	8.3	8.1	16.4	6.4	10.0
12	6.7	7.5	14.2	3.7	10.5
13	6.3	7.7	14.4	4.5	9.5
14	5.0	8.4	13.4	3.9	9.5
15	5.3	9.3	14.6	4.6	10.0
16	5.7	6.9	12.6	4.3	8.3
17	5.7	6.9	12.6	5.6	7.0
18	6.7	5.9	12.6	5.6	7.0
19	6.7	5.9	12.6	6.1	6.5
20	7.1	4.3	11.4	5.4	6.0
21	6.3	5.5	11.8	5.3	6.5

Table IX.

The Average Numbers of Paroxysms per Case per Day in the 3 Treatment Groups in 12 Severe Cases Treated 11-21 Days from the Onset of the Illness

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	8.0	11.0	19.0	1.7	17.3
2	17.4	5.6	23.0	0.3	22.7
3	15.4	9.3	24.7	4.0	20.7
4	11.8	9.9	21.7	2.7	19.0
5	12.4	8.3	20.7	2.0	18.7
6	14.6	7.1	21.7	3.0	18.7
7	14.6	8.7	23.3	9.0	14.3
8	11.8	9.9	21.7	11.0	10.7
9	7.8	12.2	20.0	8.0	12.0
10	10.8	8.7	19.5	6.8	12.7
11	8.9	9.8	18.7	5.4	13.3
12	10.3	9.7	20.0	8.0	12.0
13	9.5	7.8	17.3	6.6	10.7
14	8.9	8.1	17.0	4.3	12.7
15	11.5	1.2	12.7	1.7	11.0
16	10.1	2.5	12.6	2.3	10.3
17	9.8	1.9	11.7	1.3	13.3
18	10.5	0.8	11.3	0.0	11.3
19	9.5	0.5	10.0	0.3	19.7
20	8.8	0.9	9.7	1.8	11.5
21	5.9	2.8	8.7	0.8	9.5

Table X.

The Average Cough Index per Case per Day

in the 3 Treatment Groups for 96 Whooping Cough Patients

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	28.0	1.8	29.8	0.4	30.2
2	33.4	5.4	38.8	1.2	40.0
3	32.1	8.4	40.5	2.2	38.3
4	28.1	13.7	41.8	5.6	36.2
5	25.8	13.0	38.8	5.0	33.8
6	21.3	16.3	37.6	10.6	27.0
7	21.8	12.3	34.1	11.0	23.1
8	17.3	16.9	34.2	12.4	21.8
9	16.0	10.6	26.6	6.8	19.8
10	14.3	10.3	24.7	6.7	18.0
11	13.0	12.8	25.8	6.4	19.4
12	12.9	10.4	23.3	5.1	18.2
13	10.1	12.3	22.4	6.6	15.8
14	10.5	11.9	22.4	8.7	13.7
15	10.6	11.4	22.0	10.5	11.5
16	11.0	13.9	24.9	14.1	10.8
17	10.8	10.6	21.5	11.5	10.0
18	10.4	10.7	21.1	8.0	13.1
19	9.9	7.6	17.5	7.6	9.9
20	8.6	4.7	13.3	3.5	9.8
21	9.5	3.2	12.7	4.3	8.4

Table XI.

The Average Cough Index per Case per Day in the 3 Treatment Groups for 27 Early Cases

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	23.9	4.8	28.7	7.2	35.9
2	38.8	9.9	48.7	6.8	41.9
3	29.7	14.5	44.2	2.4	46.6
4	28.3	13.8	42.1	5.6	47.7
5	24.0	19.0	43.0	0.3	43.3
6	20.3	21.4	41.7	6.4	35.3
7	20.7	22.0	42.7	16.1	26.6
8	18.3	25.9	44.2	16.2	28.0
9	11.9	21.9	33.8	5.8	28.0
10	11.6	24.9	36.5	13.1	23.4
11	10.9	28.8	39.7	20.3	19.4
12	11.1	26.3	37.4	17.0	20.4
13	13.6	20.4	34.0	16.6	17.4
14	13.3	20.9	34.2	20.2	14.0
15	8.4	26.6	35.0	22.1	12.9
16	8.3	24.6	32.9	23.6	9.3
17	8.2	21.8	30.0	21.3	8.7
18	8.2	22.2	30.4	21.8	8.6
19	7.1	20.9	28.0	19.6	8.4
20	6.8	13.6	20.4	11.8	8.6
21	6.3	14.3	20.6	14.0	6.6

Table XII.

The Average Cough Index per Case per Day
in the 3 Treatment Groups for 47 Intermediate Cases

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	31.6	8.9	40.5	15.2	25.3
2	36.0	1.7	37.7	1.6	39.3
3	35.6	3.1	38.7	0.8	37.9
4	37.6	0.2	37.8	3.9	33.9
5	28.8	11.1	39.9	10.6	29.3
6	27.8	6.7	34.5	10.7	23.8
7	22.2	11.6	33.8	9.9	23.9
8	23.2	7.0	30.2	11.7	18.5
9	17.5	11.7	29.2	9.6	19.6
10	14.6	16.5	31.1	12.5	18.6
11	11.5	16.2	27.7	12.5	15.2
12	12.8	14.4	27.2	14.9	12.3
13	11.8	15.7	27.5	11.8	15.7
14	15.3	6.7	22.2	11.3	10.7
15	18.3	6.7	25.0	14.7	10.3
16	13.3	10.0	23.3	14.0	9.3
17	13.6	11.7	25.3	14.5	10.8
18	13.4	10.7	24.1	12.8	11.3
19	11.3	7.7	19.0	9.9	9.1
20	9.7	4.0	13.7	6.0	7.7
21	7.5	5.9	13.4	6.1	7.3

Table XIII.

The Average Cough Index per Case per Day
in the 3 Treatment Groups for 22 Late Cases

Day	Chloramphenicol	Difference	Control	Difference	Aureomycin
1	23.3	2.3	21.0	12.6	33.6
2	26.0	6.0	32.0	8.3	40.3
3	22.0	6.1	28.1	2.5	30.6
4	19.7	9.2	28.9	3.6	32.5
5	18.2	11.8	30.0	1.4	28.6
6	18.2	6.3	24.5	0.5	25.0
7	19.5	7.0	26.5	4.7	21.8
8	16.3	7.6	23.9	3.6	20.3
9	16.7	2.6	19.3	0.6	19.9
10	15.7	0.6	16.3	5.1	21.4
11	14.5	1.7	12.8	5.6	18.4
12	10.5	3.4	13.9	3.7	17.6
13	12.8	0.7	12.1	1.6	13.7
14	8.5	4.6	13.1	0.3	12.8
15	8.3	3.7	12.0	0.5	11.5
16	10.2	1.1	11.3	0.9	10.4
17	8.0	2.6	10.6	0.5	11.1
18	6.1	1.2	7.3	2.4	9.7
19	5.7	0.4	6.1	3.4	9.5
20	6.5	1.9	4.6	4.7	9.3
21	6.0	0.1	5.9	2.1	8.0

Table XIV.

The Number of Paroxysms per Day in Five Cases Treated with Chloramphenicol in whom there is a Relapse

Day	Case No. 1	Case No. 2	Case No. 3	Case No. 4	Case No. 5
1	10	7	5	14	29
2	13	20	9	12	30
3	16	11	17	14	27
4	13	13	19	13	23
5	19	10	19	10	24
6	17	13	8	7	23
7	12	8	6	5	24
8	11	9	9	7	28
9	7	7	3	8	23
10	7	15	0	9	25
11	6	12	1	11	19
12	8	12	3	13	13
13	10	15	4	12	12
14	11	10	10	15	10
15	13	9	10	12	13
16	19	7	9	10	24
17	29	5	9	9	21
18	16	5	8	7	24
19	10	6	5	6	20
20	8	7	6	4	19
21	6	5	4	4	16