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STREPTOMYCIN IN OPHTHALMOLOGY

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Tuberculous lesions of the eye and infections by Gram-negative bacilli constitute the two groups for which streptomycin therapy would be indicated on theoretical grounds. The cases diagnosed as tuberculous are a composite group. Tubercle bacilli, or typical giant-cell formation, can be demonstrated in tuberculous conjunctivitis, but for the mass of lesions diagnosed as tuberculous keratitis and tuberculous iritis no such definite evidence is generally available. The diagnosis in such cases is usually on clinical grounds, with very variable supporting evidence. As for infections by Gram-negative bacilli, these are on the whole infrequent, the outstanding examples being infection of the cornea by *Pseudomonas pyocyanea* and by *Proteus vulgaris*. Here bacteriological evidence is readily available. Apart from being easily established bacteriologically, the clinical picture that these Gram-negative bacilli give in the cornea is characteristic. Instead of the classical serpiginous corneal ulcer and hypopyon, there is a corneal ulcer with a sloughy base, frequently heaped up, and generally extending as infiltrates well into the surrounding corneal tissue; hypopyon is not a characteristic concomitant, but is not exceptional and is apt to appear very dense. These corneal infections do not respond to the sulphonamides or penicillin, and they run a rapid and disastrous course, often leading to opacification of the whole of the cornea and to perforation.

It is generally accepted that tuberculosis of the conjunctiva, cornea, iris, and retinal veins is secondary to a general infection. This does not exclude local therapy as an agent of some value, but does emphasize that exclusively local therapy is unlikely to prove satisfactory. In the case of infections with Gram-negative bacilli the lesion is exclusively local, and local treatment may therefore be expected to give the desired results.

In the present study an attempt has been made to establish the levels of concentration that can be reached in the eye by the systemic and subconjunctival injection of streptomycin; the efficacy of such administration in experimental infection of the cornea by *Ps. pyocyanea* has been investigated; and we have tried to evaluate the use of streptomycin clinically.

Experimental Studies

(a) Ocular Tolerance of Streptomycin Injected Subconjunctivally

The purified streptomycin salt at present available is soluble to the extent of 0.5 g. in 1 ml. of water. The solution thus obtained is well tolerated by the rabbit when injected subconjunctivally—in fact, very much better than 1,000,000 units of penicillin similarly given.

There is nothing to be gained by giving smaller doses subconjunctivally. Larger doses cannot be given, as more than 0.5 g. does not go into solution in 1 ml.

(b) Levels of Concentrations Reached in the Eye by the Systemic and Subconjunctival Injection of Streptomycin

Method.—Rabbits weighing 2.5–3 kg. were used for the tests. Dihydrostreptomycin sulphate was injected in three ways: (1) 50 mg. per kg. was injected in 2 ml. of physiological saline intramuscularly; (2) 500 mg. was injected in 1 ml. of distilled water subconjunctivally; and (3) 500 mg. was injected in 1 ml. of 1:1,000 adrenaline subconjunctivally. At appropriate times the animals were killed by the intravenous injection of pentobarbitone sodium and the eyes removed. In the case of the animals treated by intramuscular injection, both eyes were taken and treated as one. They were given a rapid rinse in sterile saline and were then immediately dissected. The aqueous humour, vitreous humour, anterior tissues, posterior tissues, and cornea were separated, minced with scissors, and after weighing were extracted with an appropriate amount of pH 8 phosphate buffer. Samples of blood were removed from the left ventricle of the animals just before death. The extracts and the blood samples were titrated for streptomycin content by either the capillary-tube method with *Bact. friedländeri* or by plate assay method using *Bacillus subtilis*.

The results are recorded in Table I.

The following points may be noted: (1) Intramuscular injection of 50 mg. per kg. in the rabbit is equivalent to approximately an intramuscular injection of 4 g. in an adult patient—well beyond the toxic limit. With this dose it will be noted that levels at four hours and subsequently are *nil* in the vitreous and cornea, whilst the aqueous gives a level of only 0.3 µg. at four hours. The levels at two hours are also not high. (2) A subconjunctival injection of 500 mg. in 1 ml. of water gives considerable levels in the aqueous and vitreous,

TABLE I.—Ocular Concentrations of Streptomycin in the Rabbit After Administration by Different Routes

Route and Dose	Time (hours)	Streptomycin Levels ($\mu\text{g./ml.}$ or $\mu\text{g./g.}$)					
		Blood	Aqueous	Vitreous	Ant. Tissues	Post. Tissues	Cornea
Intramuscular; 50 mg. kg.	2		1.3	0.5			Trace
	4		0.3	0			0
	6		0	0			0
	8		0	0			0
Subconjunctival; 500 mg. in 1 ml. water	2	254	14.0	7.0	360	230	35.0
	4		9.5	<2.2			460
	6		6.0	4.0			7.5
	12	9.0	4.0	<1.1	6.0	7.5	12.5
	16		1.6	1.0			<0.5
	18	0.57	1.44	<0.37	<1.85	<1.85	<3.7
	20		0	0			0
	24	0.26	<0.4	<0.2	<1.0	<1.0	<1.0
Subconjunctival; 500 mg. in 1 ml. 1:1,000 adrenaline	2	190	156	190	4,000	3,000	1,575
	4		64				128
	6		<16				25
	12	17.0	13.5	<2.2	30	38	32
	16	5.3	164	2.3	164	47.5	282
	24		>28				3.5
	28	1.5	264	15.3	112	30	900
	36		>40				3.3
	48		87.5	4.53	117	57	283
		<0.62	<0.74	<0.37	3.1	10.25	<1.85
		<0.2	<1.0	<1.0	2.15	1.9	<2.0
		<0.2	<0.4	<0.2	3.12	7.0	<1.0

persisting for about 12 hours. (3) A striking feature is the markedly increased initial intraocular concentrations when streptomycin is dissolved in adrenaline 1:1,000 instead of water, and the considerably longer persistence of these levels: at 36 hours the levels are still significant.

These findings are of the same order as those recorded for penicillin: subconjunctival injection gives higher levels than intramuscular injection, and the levels become both higher and more persistent when adrenaline is added to the solvent.

(c) Experimental Infection of the Cornea with *Ps. pyocyanea*

Method.—Thirteen rabbits were used. The cornea of the right eye of each rabbit was scarified with a scalpel blade and infected with two loopfuls (3-mm. diameter loop) of a suspension of *Ps. pyocyanea* (24-hour agar culture of strain 150 E), the suspension being rubbed into the scarified area with the loop for about 15 seconds. Three of the animals were kept as controls. The remaining 10 were treated three hours after infection by the injection, subconjunctivally into the infected eye, of 0.5 g. of dihydrostreptomycin sulphate in 1 ml. of 1:1,000 adrenaline. A single dose only was given. The course of the infection

was followed in all of the animals by daily inspection. The heavily infected control animals were killed on the sixth day, when the corneae had perforated.

The results in this experiment are summarized in Table II.

It will be seen that the three control animals all showed the disastrous course characteristic of *Ps. pyocyanea* infection in the rabbit. The 10 animals treated with a single subconjunctival injection of 0.5 g. of streptomycin in adrenaline 1:1,000 gave eminently satisfactory results. By the third day only two of these ten had not recovered fully. By the fifth day one of these two had become normal. The damage in the one animal that had not responded fully was almost negligible.

Clinical Experiences

The clinical results recorded here have been collected over the past three years. In the earlier stages purified streptomycin was not available and dosage was hampered by irritative reactions. In all, streptomycin was used systemically or locally in 53 cases, which fall into four clinical groups:

Group I.—Cases with a definite bacteriological or histological diagnosis. These comprised tuberculous conjunctivitis, acute conjunctivitis, dacryocystitis, infected corneal ulcer, and one case of intraocular infection, all due to Gram-negative bacilli or to penicillin-resistant organisms.

Group II.—Cases presumed to be tuberculous on good clinical grounds. This group consisted of three cases of tuberculous keratitis.

Group III.—Cases presumed to be tuberculous on indefinite clinical grounds—Eales's disease, iridocyclitis, and scleromalacia perforans.

Group IV.—Cases of tuberculous allergy—phlyctenular ophthalmia.

Group I. Cases with Definite Histological or Bacteriological Diagnosis

(a) *A Case of Tuberculous Conjunctivitis.*—A child aged 5½ had a large sloughing ulcer in the inferior fornix of the left eye; biopsy showed it to be tuberculous, with tuberculous giant-cells and caseation; tubercle bacilli were demonstrated in the smear of the guinea-pig inoculation. Treatment with intramuscular streptomycin, 0.5 g. a day for 30 days, caused rapid resolution of the lesion clinically, but, histologically, cure was much slower. Biopsy three months later showed fibrous tissue with a few epithelioid cells, while guinea-pig inoculation

TABLE II.—Treatment of *Ps. pyocyanea* Infections of the Cornea in Rabbits with Dihydrostreptomycin Sulphate in Adrenaline

Rabbit No.	Treatment	Appearance of Infected Eye after Infection			
		3 Days	5 Days	6 Days	19 Days
1	Control untreated	Leucoma of cornea in 3 mm. diam. zone at site of infection	Mild central opacity with peripheral vascularization. Commencing panophthalmitis	Perforation of cornea. Animal destroyed	
2	" "	Complete opacity of cornea with pus in anterior chamber	Complete corneal opacity with grey infiltration. Useless eye	" "	
3	" "	Complete opacity of cornea with conjunctival and corneal ulcer	Staphylococcal cornea with hypopyon. Useless eye	" "	
4	Treated with 0.5 g. streptomycin in adrenaline	Eye normal	Eye normal. Some slight lid reaction due to streptomycin		Eye normal
5	" "	" "	Eye normal		" "
6	" "	" "	" "		" "
7	" "	" "	" "		" "
8	" "	" "	" "		" "
9	" "	Slight corneal opacity, not at the spot where infected. Slight conjunctivitis with discharge	Very slight corneal haze. Otherwise normal eye		Slight corneal opacity
10	" "	Eye normal	Eye normal		Eye normal
11	" "	" "	" "		" "
12	" "	Very slight corneal opacity. Some lid reaction	" "		" "
13	" "	Eye normal	" "		" "

was negative. When seen recently, 18 months later, there was no sign of the lesion beyond fibrosis, and there had been no relapse.

(b) *Six Cases of Acute Conjunctivitis*.—All cases were due to *Proteus vulgaris* except one case, which produced a penicillin-resistant staphylococcus after prolonged local penicillin therapy. Four cases were initially treated by other drugs which had no effect; two cases, in which the smear showed Gram-negative organisms, were started on streptomycin immediately. Two cases were treated with drops (in a concentration of 0.5 g. per ml. instilled at half-hourly intervals), three with ointment (0.1 g. per g.), and one, following a cataract extraction, with subconjunctival streptomycin (0.5 g. in 10 min. (0.6 ml.) of water and 5 min. (0.3 ml.) of adrenaline 1:1,000). All cases cleared up quickly. The results were comparable to those seen with local penicillin therapy in conjunctivitis due to penicillin-sensitive organisms.

(c) *A Case of Acute Dacryocystitis*.—This was a severe recurrence of a typical acute dacryocystitis which did not respond to four days of systemic penicillin, in the last two of which the sac was also syringed with penicillin. Systemic streptomycin therapy (0.5 g. a day for five days) led to a rapid and uninterrupted recovery, the sac remaining patent. The organism proved to be *P. vulgaris*.

(d) *Nine Cases of Infected Corneal Ulcer*.—Six cases occurred within five days of having had a corneal foreign body; one was an ophthalmia neonatorum; one was a secondary infection of a dendritic ulcer; and one was a case of marginal ulcer of unknown cause. The organisms in these nine cases were *Ps. pyocyanea* in two cases, Gram-negative bacilli in three cases, and *P. vulgaris*, *Bact. coli*, *B. xerosis*, and bacillus of Patel in one case each. All but two cases were given daily subconjunctival injections of 0.5 g. of streptomycin within two or three days of the start of infection; one case had been worsening for three months, and in the other, the baby with ophthalmia neonatorum, treatment by drops and intramuscular injection was started 10 days after onset, there having been very slight improvement on systemic sulphonamide for six days. Two cases had been started on streptomycin immediately, one having been diagnosed as a Gram-negative type of infection clinically and confirmed bacteriologically next day, 24 hours thus being saved; while the other showed Gram-negative bacilli in the smear. Five cases had one dose of subconjunctival penicillin (1,000,000 units) on admission, the nature of the infection not being known till 24 hours later, from the culture. The conjunctiva became friable after repeated subconjunctival injections, and, when it would hold no more, streptomycin was given retrobulbarly. This is probably less effective.

The Subconjunctival Injection.—The dose was at first 1 g. of streptomycin in 2 ml. of fluid, but this has been reduced to 0.5 g. in 1 ml. The solvent used is as for subconjunctival penicillin—a stock solution, 10 min. (0.6 ml.) of which contains 1/40 gr. (1.6 mg.) of atropine sulphate and 1/8 gr. (8 mg.) of cocaine hydrochloride. To 10 min. (0.6 ml.) of this solution is added 5 min. (0.3 ml.) of adrenaline 1:1,000 before injection.

Results.—All cases were left with a quiet eye, except the one which was hopeless to begin with and became quiet only after perforating. Three cases had a poor visual result of 3/60 or less, due to dense corneal scarring owing to the severe initial damage before streptomycin treatment was instituted. The remaining

cases obtained a good visual result, the corrected visual acuity being 6/9, 6/12, and 6/12 in three cases, and 6/36 under a mydriatic in a patient who could not be followed up. The baby with ophthalmia neonatorum had a thin residual scar.

(e) *A Case of Post-operative Intraocular Infection*.—A man with a right detached retina had a lens extraction for traumatic cataract in the other eye while under systemic penicillin and local treatment to control an intractable otorrhoea. Forty-eight hours after operation subconjunctival streptomycin, 0.5 g., and systemic streptomycin, 0.5 g., were started, as the anterior chamber was infected; treatment was continued for five days. The infection subsided and some useful vision may be expected after needling.

Group II. Cases Presumed to be Tuberculous on Good Clinical Grounds

Three Cases of Tuberculous Keratitis.—Three typical cases with long histories were treated for one or two months with between 2 g. and 0.5 g. of intramuscular streptomycin daily, the dosage tending to decrease while the duration of the course tended to increase. All cases improved markedly within a fortnight, and in one case the result was particularly striking: the visual acuity improved from hand movements in both eyes to 6/60 in the right eye and 6/9 in the left eye—very much better than it had been for years. These three cases have now remained quiet for periods of 10, 19, and 26 months respectively.

Group III. Cases Presumed Tuberculous on Indefinite Clinical Grounds

(a) *Four Cases of Eales's Disease*.—Four cases presented as Eales's disease: only one case showed (in a chest radiograph) any further evidence of tuberculosis. These patients were given systemic streptomycin for one or two months, with between 2 g. and 0.5 g. of intramuscular streptomycin daily, the dosage tending to decrease with a longer course. The results are dubious and indefinite. The most that can be claimed is the absence of relapses in three cases which seemed quiet or quiescent at the start, while the one active case has become worse.

(b) *Five Cases of Iridocyclitis*.—Four of these five cases had a common history of slowly worsening iridocyclitis for over six months, with the development of mutton-fat K.P., before streptomycin was started; in the remaining patient there was a history for only two months. Two of these cases had further indications of a possible tuberculous origin—tuberculous pleurisy in the one, and a strong family history of tuberculosis in the other. Two patients, both young women, developed retinal vasculitis. All received one dose of streptomycin, 0.5 g. a day for a month intramuscularly, except one patient who had side-effects necessitating its discontinuance after 17 days. One patient has shown only slight improvement, and it is now three months since she had the course; another became completely clear only seven months after the course; two patients who developed secondary glaucoma and pain just before the course had (three months later) normal tension and no pain, and the K.P. had become thinner and crenated. The patient who had had an incomplete course owing to toxic effects now has only a slight aqueous flare in both eyes, but, as she responded to x-ray therapy shortly after the streptomycin was discontinued it is impossible to say to which treatment (if to either) her improvement should be attributed.

(c) *Iridocyclitis with Nodules*.—Of three cases, one, that of a woman aged 20 with multiple nodules in one iris—the whole reaction strongly suggestive of sarcoidosis—showed no response to systemic administration of streptomycin. The two other cases, with an isolated nodule in each instance, appeared to improve. Steady diminution of the nodule was observed during a month's treatment by intramuscular injections of 0.5 g. daily, but the improvement has not been maintained. In one case the nodule is still as large as before, and in the other there is a recurrent iridocyclitis.

(d) *Three Cases of Scleromalacia Perforans*.—These cases, which had been progressing steadily, were given 0.5 g. of streptomycin systemically six-hourly for 28 to 56 days. In none was there any improvement.

Group IV. Cases of Tuberculous Allergy : Phlyctenular Ophthalmia

Children with phlyctenular ophthalmia were found to improve quickly on mydriasis and an open-air regimen at White Oak Hospital. Seventeen cases were given systemic streptomycin in addition, because they either showed no response or relapsed repeatedly. Fourteen cases had active lesions when the course was started—nine for at least two months and five for three weeks or less. Four of these children had long histories of repeated relapses. In addition streptomycin was given to two cases which had shown frequent relapses but were then quiet, and to one case which was almost quiet before the course started.

The diagnosis, made on clinical grounds, was supported in 15 cases by one or more of the following features : positive Mantoux reaction, a positive chest x-ray finding, and a family history of tuberculosis.

At first streptomycin was given on a basis of 20 mg. per lb. (0.45 kg.) body weight a day in divided doses for a week, but later in the investigation the amount of the drug was reduced, and it was given in one daily dose over a longer period, the ultimate dosage used being 10 mg. per lb. (0.45 kg.) a day for 56 days.

In the acute case streptomycin proved of value in cutting short the acute attack and possibly also in preventing recurrences. The results in the 14 active cases may be tabulated as follows :

Activity under Control Within	No. of Cases	Relapses Within 3 Months	No. of Cases	Follow-up Results After First 3 Months of 13 Controlled Cases	
				Quiet for	No. of Cases
7 days ..	2	No relapse	5	24–28 months	3
10 " ..	5	One "	3	18–24 "	3
21 " ..	4	Two relapses	3	12–18 "	3
28 " ..	1	Three "	2	Relapse: a year later	1
56 " ..	1	Uncontrolled	1	Not known—trace lost	3
Uncontrolled..	1				
	14		14		13

The results in the three cases treated during the quiescent stage in the hope of controlling their tendency to frequent relapses were : (1) Frequent recurrences for the 21 months under observation in one case, but the attacks were probably milder. (2) Three relapses in the two months following the course and three more in the four months subsequent to a second course. Since then quiet for 18 months. (3) No relapse for four months after a course of treatment—in contrast to three attacks in two months before treatment.

Discussion

The excellent results achieved with penicillin in infections of the eye due to penicillin-sensitive organisms have thrown into sharp relief those infections, largely due to Gram-negative bacilli, for which penicillin is ineffective. Some cases of acute conjunctivitis and acute dacryocystitis are caused by penicillin-insensitive organisms, but the more threatening of the acute lesions is infection of the cornea by Gram-negative bacilli. These run a rapidly destructive course, for the corneal reaction is essentially a proteolytic phenomenon consistent with the proteolytic properties of these organisms.

The recognition of Gram-negative infection of the cornea as a characteristic clinical entity calling for specific treatment appears to have been anticipated by the older literature. The concept of corneal abscess of the older literature does not seem to have been well defined, the term being used for corneal ulceration with diffuse infiltration as well as for interstitial corneal reaction without ulceration. It is likely that what went under the name of corneal abscess included the group of infections of the cornea by Gram-negative bacilli stressed here. In so far as it emphasizes the interstitial reaction of the cornea, that designation was most useful. The complete clinical picture appears, however, to require equal stress on the sloughy, heaped-up base of these corneal ulcers.

The experimental evidence from infection with *Ps. pyocyanea* that such infected ulcers respond well to streptomycin is supported by the limited clinical experience reported here, and it may be assumed that with early and adequate streptomycin treatment these corneal infections will respond as readily as serpiginous ulceration responds to penicillin. Whilst the experimental results were obtained with 1 ml. of adrenaline as the solvent, clinically it would not be safe to use so much adrenaline. For this reason it would be best to use 10 min. (0.6 ml.) of water and 5 min. (0.3 ml.) of adrenaline. The solvent can readily be adjusted to give a mydriatic effect by incorporating 1/8 gr. (8 mg.) of cocaine hydrochloride and 1/40 gr. (1.6 mg.) of atropine sulphate in the 10 min. (0.6 ml.) of water. A stock solution containing these ingredients is easily prepared, and keeps well, but it is essential that the adrenaline should not be added to the solvent until use.

The value of streptomycin in the tuberculous infections of the eye is not so definite, if only because diagnosis is frequently uncertain. Judging by the proved case of tuberculous conjunctivitis recorded here, as also by the cases of presumed tuberculous keratitis, systemic treatment is of considerable help. Whether these cases should not in addition be treated by local applications is an open question. The results in phlyctenular ophthalmia are also hopeful. Here there seems less reason for local treatment. The disappointing results obtained in plastic and nodular iritis, presumed to be tuberculous in origin, and in Eales's disease, may arise from inadequate use of streptomycin or from a fallacious aetiological interpretation.

Summary

Streptomycin, 0.5 g. in 1 ml. of water, is well tolerated on subconjunctival injection.

Such doses give considerably higher intraocular levels when injected subconjunctivally than on intramuscular injection.

The intraocular levels are higher still and persist up to 36 hours if adrenaline 1:1,000 is the solvent.

In the experimental animal a destructive *Ps. pyocyanea* infection of the cornea is fully controlled by one subconjunctival injection of 0.5 g. of streptomycin in 1 ml. of adrenaline 1:1,000.

For clinical purposes streptomycin to be injected subconjunctivally should be dissolved in 10 min. (0.6 ml.) of water to which 5 min. (0.3 ml.) of adrenaline 1:1,000 is freshly added.

Clinically, streptomycin is effective when used subconjunctivally in infections of the cornea due to Gram-negative bacilli. As these lesions are highly destructive, early treatment is essential, and the characteristic clinical appearance of such infections facilitates early diagnosis. Streptomycin locally is also invaluable in acute conjunctivitis due to Gram-negative bacilli.

Systemic streptomycin therapy has proved helpful in tuberculous keratitis. It has given poor results in presumably tuberculous iridocyclitis and in periphlebitis. In phlyctenular ophthalmia it tends to cut short severe attacks, and probably reduces the frequency and severity of relapses.

Our thanks are due to Dr. P. D'Arcy Hart and the Medical Research Council for liberal supplies of streptomycin during the earlier stages of this investigation, when the material was not readily available. We are obliged to Sister Thorogood and her staff of the Royal Eye Hospital unit at Lambeth Hospital and to Sister Condon, formerly of White Oak Hospital, for their help in the treatment of patients. To Dr. P. Muggleton and Mr. B. I. Helliwell, of Glaxo Research Laboratories, we are indebted for technical assistance.

THE CLINICAL FEATURES OF THE PNEUMONIAS UNDERGOING VIRUS TESTS

BY

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The response of the pneumonias to sulphonamides and penicillin has broadened rather than solved the problem of the differential diagnosis and treatment of lung consolidations. Since such treatment has been introduced, a wide group of non-bacterial pneumonias caused by viruses and rickettsias has been revealed. American authorities have stressed the increasing incidence of virus pneumonias, Goodrich and Bradford (1942) finding them almost as frequent as pneumococcal pneumonias, and Reimann (1943) computed figures of 70% of all pneumonias for this group. The process of sorting out the various non-bacterial pneumonias is not yet far advanced, and while influenzal pneumonias and the pneumonias of psittacosis, lymphocytic choriomeningitis, glandular fever, lymphogranuloma venereum, and Q fever have emerged as definite entities other similar pneumonias await identification.

The group of "primary atypical pneumonia, aetiology unknown," has been considered by some as an entity (Joules, 1950), but this has been denied elsewhere (Scadding, 1948). In the last-named condition the non-specific cold agglutination reaction has been used as a diagnostic test; in the other pneumonias mentioned the diagnosis is confirmed by the detection of specific antibodies by complement-fixation and neutralization tests. A rise in antibody titre in these tests is diagnostic and is

particularly valuable in influenza, in which it is often impossible to obtain the virus from the patient's nose or throat and so to isolate it by ferret inoculation.

The complement-fixation test was the one employed in the series of cases described below, and most of the cases were also examined for complement-fixing antibodies of *Rickettsia burneti*, psittacosis-ornithosis and lymphogranuloma viruses, and by *Streptococcus M.G.* agglutination. Where possible the tests were done on acute and convalescent phase sera, but in some cases only convalescent sera were obtainable. These tests were performed by Dr. B. P. Marmion, Dr. A. D. Macrae, and Dr. A. P. Goffe, of the Colindale Group Laboratory. Cold haemagglutination tests were also done on many of the cases at the Edgware General Hospital by Dr. E. D. Hoare. Nearly every case was questioned and examined by me so as to obtain a uniform approach to the clinical aspects of these cases of pneumonia. This paper is a review of the clinical findings in 159 of such cases seen in the Edgware General Hospital between the beginning of January, 1949, and the end of May, 1950.

Clinical Investigation

It soon became apparent that clinical methods did not readily distinguish the various forms of pneumonia, so all cases of suspected lung consolidation seen during the investigation were serologically tested. The cases are divided into two groups, the first being seen between January 1 and September 1, 1949, and the second group between early November, 1949, and the end of May, 1950. A fairly severe outbreak of influenza (mainly of the A type) is included in the first group, and the second group covers a lesser outbreak of influenza B in March and April, 1950. While the patients were being submitted to the tests just mentioned special consideration was also given to certain features: the history and symptoms of the illness; a past history of chest infection; the signs of the illness; the duration of the fever; the x-ray findings; the white cell counts; the sputum examinations; and the nature of any complications.

The two groups showed very similar numbers of cases, 88 being examined in the 1949 group, and 71 in the 1949-50 group. The cases were all of severe respiratory disorder, and either showed clear pneumonic signs or had such symptoms of lung involvement that pneumonia was immediately suspected. The patients had all been active till the onset of the illness, even though some had old respiratory or cardiac disease, and the rapid development of severe symptoms, often of sudden onset, was a feature in all. The composition of the two groups as determined by the special tests is shown in Table I, the

TABLE I

	Group 1 (1949)	Group 2 (1949-50)
Influenza (confirmed)	16	18
(probable)	22	—
Primary atypical pneumonia	11	11
Psittacosis-ornithosis	—	2
Unclassified	39	40
Total	88	71

"primary atypical pneumonias" being the cases in which a cold agglutinin titre of 1 in 16 or over was reached. The cases classified as definitely positive influenzas were those which showed a rise of influenza antibody titre between the acute and convalescent phases; if a signifi-