PNEUMONIA IN NORTH-WEST LONDON, 1942-4

II. PNEUMONIAS NOT ATTRIBUTABLE TO SPECIFIC BACTERIAL INFECTION

BY

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In a preceding paper Humphrey, Joules, and van der Walt (1948) described a series of 351 patients with primary pneumonia admitted to the Central Middlesex County Hospital, between July, 1942, and April, 1944, and presented especially the findings in the 298 patients with pneumonia attributed to pneumococci or to other accepted pathogenic bacteria. This paper is concerned with the remaining 53 patients (15 per cent) in the series, in whom the pneumonia could not readily be assigned on clinical, bacteriological, and radiological evidence to either of the above groups, but was assigned to a rather heterogeneous third group of pneumonias not attributable to specific bacterial infection. It was not until we had reviewed the first hundred cases of the series that it became apparent that the aetiological classification of the large proportion of cases which could not be attributed to bacterial infection was a serious problem, and it was decided to seek for evidence of virus infections, both by serological means and by direct attempts to recover viruses by inoculation into animals. The clinical data therefore are derived from 351 cases, while the remaining data apply to the last 250 cases only.

CLINICAL FINDINGS

The group certainly included widely different conditions, ranging from "bronchopneumonia" in a chronic bronchitic patient on the one hand to cases which were obviously due to disease processes quite unlike those found in the common bacterial pneumonias. In Table I are listed the chief differences between this group and the group of pneumococcal pneumonias. There were no significant differences between the two groups in respect of age and sex distribution; history of previous chest disease (approximately 40 per cent in both groups); physique; rate of radiographic clearance. The monthly incidence has been set out in the previous paper and showed no unusual seasonal incidence such as has been found for

"primary atypical pneumonia" (Dingle and others, 1944). The differences lay rather in a tendency to relatively insidious onset; failure to respond rapidly to sulphonamide therapy; absence of pathogenic bacteria from the sputum; patchy, mottled shadows, usually involving more than one lobe, in the chest radiograph; and, in some cases, a tendency for the disease process to migrate from one lobe to another. On admission the patients were, in general, not so severely ill as those with pneumococcal pneumonia, nor did the majority have leucocytosis, but the disease subsided more slowly, as judged by temperature and erythrocyte sedimentation rate (E.S.R.) determinations, and there was a greater tendency to form sterile pleural effusions. It should be stated here that, compared with patients seen by us later with undoubted "primary atypical pneumonia," none of this group showed the clinical picture of headache and dry, unproductive cough characteristic of the early stages of this disease.

Of the 53 patients in the group, only 15 had received sulphonamide drugs before admission to hospital; ten had less than 10 g., and five had more than 10 g. For this reason it is unlikely that any considerable number represent cases of pneumococcal pneumonia which had been insufficiently treated at home and were admitted during a stage of partial resolution, with their infecting organisms rendered sulphonamide-resistant as a result of treatment.

In the course of this investigation and in the subsequent two years we have come to recognize a small group of wandering pneumonias, not responsive to chemotherapy and giving serological evidence of infection with a virus of the psittacosis type, and more recently another group which fits the description of "primary atypical pneumonia" widely described in the U.S.A. and elsewhere. It must be emphasized, however, that these groups are small compared with the total of pneumonias of unassigned aetiology, and the

TABLE I

DIFFERENCES IN CLINICAL AND LABORATORY FINDINGS BETWEEN FIFTY-THREE CASES OF PNEUMONIA OF UNCERTAIN AETIOLOGY AND 278 CASES OF PROBABLE PNEUMOCOCCAL PNEUMONIA

	Pneumonias of uncertain aetiology (%)	Pneumococcal pneumonias (%)
<i>History and onset</i>		
Ill for more than 6 days before admission	60	20
Onset with malaise and cough only	88	45
Onset with rigors and pleural pain	12	53
<i>Clinical course</i>		
Number of lobes involved 1	35	69
" " " 2	61	26
" " " more than 2	4	5
Temp. more than 99° F. 4 days after admission	67	38
" " " 7 days after admission	35	20 (14)*
Temp. over 103° F. on admission	33	41
Average duration of pyrexia from onset of disease	16 days	10.3 (9.1)* days
Pleural pain	65	90
Sterile effusion	23	5
Infected effusion	0	4
<i>Laboratory findings</i>		
Leucocyte count on admission less than 12,000 per c.mm.	56	27
E.S.R. more than 20 mm. in 1 hour at 12 days	65	51
" " " 1 month	19	12 (4)*
" " " isolated	12	71
<i>X-ray findings</i>		
Lobar consolidation	39	69
Mottled consolidation, wandering consolidation, etc.	61	31

* Figures in brackets are for pneumococcal pneumonias, omitting those which had frank empyemata, abscesses, etc. These figures give a more valid comparison, since pyogenic complications are excluded.

latter have shown no such striking similarity from case to case as is found in a series of frank lobar pneumonias. This is best shown by some illustrative case histories, which are given in an appendix.

LABORATORY FINDINGS

BACTERIOLOGICAL

A discussion of the chief bacteriological findings in the sputum, and of their significance, has been given in the previous paper. The most significant finding was perhaps that of *Staph. aureus* in 11 (21 per cent of the sputa, in contrast to 5 per cent of sputa of the pneumococcal group, since it suggests that a few of the cases of uncertain aetiology may have been primary staphylococcal pneumonias.

"Non-pathogenic" organisms (α - and γ -haemolytic streptococci)

Strep. viridans has been proved to be an occasional cause of pneumonia, and wherever the proof has been adequate the pneumonia has been very severe (Solomon and

Kalkstein, 1943). We isolated α -haemolytic streptococci, which were not further investigated, from 61 per cent of sputa examined. They were frequently the predominant organisms, but since they were never isolated from other body fluids and are known to be common saprophytes in the nasopharynx, there is no proof that they were pathogenic. The proportion of sputa containing α - and γ -haemolytic streptococci was constant from season to season.

Non-haemolytic streptococci were obtained from 15 per cent of sputa, with no marked variation in incidence from group to group of our classification. A particular strain of non-haemolytic streptococci, M.G., has been obtained from the lungs at autopsy in certain cases of primary atypical pneumonia (Mirick and others, 1944), and antibodies to this strain were developed in the majority of patients with primary atypical pneumonia in their series, and in that of Finland and others (1945). There is no evidence, however, that non-haemolytic streptococci are a primary cause of pneumonia, and the same objections apply to classifying them as pathogens as apply to

α -haemolytic streptococci. Nevertheless it is possible that in bronchi and bronchioles damaged by chronic bronchitis, or in a lung whose resistance is lowered by preceding virus infection, these organisms may have been the cause of the persistence of pneumonic changes.

LUNG PUNCTURE.—Lung puncture, by aspiration through a No. 5 needle inserted 4 to 7 cm. deep into the chest at a site where physical signs were maximal, was performed in 25 cases, all of which were atypical. The scanty aspirated material, which usually consisted mainly of blood, was used for making smears stained by Gram and Leishman methods, and was inoculated immediately on to blood agar plates and into broth. In certain instances it was used for animal inoculation. In only one instance was a positive culture obtained, when pneumococci were grown from an area of persistent consolidation in a woman who had ceased to bring up sputum. The stained smears yielded only negative information, and although no complications resulted from the procedure we were not convinced that lung puncture as performed was of sufficient diagnostic value to justify its continuance.

SEROLOGICAL INVESTIGATIONS

At the time of this investigation there appeared to be rather few viruses which were likely to give rise to pneumonic conditions in our patients. The most obvious, excepting influenza (which in its uncomplicated form does not give radiographic changes in the lungs), were the so-called "primary atypical pneumonia" and the psittacosis group. Lymphocytic choriomeningitis was also included for a period, since in experimental monkeys this virus can give rise to pulmonary consolidation, and it is a disease not too infrequently (though possibly wrongly) diagnosed in patients in the London area.

PRIMARY ATYPICAL PNEUMONIA

Serum cold agglutinins

Although it is clear that early descriptions of atypical pneumonia include a variety of different virus pneumonias (Reimann, 1945), a number of investigators have noted that well-defined outbreaks of "primary atypical pneumonia" and the experimental transmission of this disease to human volunteers (Dingle and others, 1945) have been accompanied by marked rises in the cold agglutinin titres of the sera of one-third to one-half of the patients. Turner and his colleagues (1943), who made the first observations in Great Britain (among U.S. Army personnel), found that in 83

unselected cases more than half had an agglutinin titre of 1:32 or higher, whereas in a parallel series of other miscellaneous respiratory diseases the titres rarely exceeded 1:16. Agglutinin titres were maximal between the tenth and twentieth days of illness, and then gradually fell away. The subject of cold agglutination has been well reviewed by Stats and Wasserman (1943), who give a detailed account of other conditions in which cold agglutinins are notably found in the serum. These include trypanosomiasis, hepatic cirrhosis, staphylococcal septicaemia, leukaemia, etc., none of which are common enough to confuse findings in pneumonia patients. There is little doubt that routine estimation of cold agglutinins on acute and convalescent sera from pneumonia patients should enable half the cases of the "primary atypical pneumonia" in question to be picked out.

Results

We used the method of Turner and others (1943), which consists in effect of allowing serial twofold dilutions of serum to stand overnight at 4° C. with a 1 per cent suspension of fresh washed human red cells of group O (IV). The macroscopic end point only is recorded, and also the formation of a solid clump of agglutinated cells, which was reckoned by Turner to be particularly significant. Tests were made on sera from all the cases of pneumonia of uncertain aetiology in the last 250 patients and from a number of cases of known bacterial pneumonia. All sera were kept sterile at 4° C. and were tested within fourteen days of being taken. The results are given in Table II and show that in only two cases was a significant titre found. One of these had myeloid leukaemia and must be discounted.

TABLE II

SERUM COLD AGGLUTININ TITRES IN SEVENTY UNSELECTED CASES OF PROVED BACTERIAL PNEUMONIA AND TWENTY-FIVE CASES OF UNCERTAIN AETIOLOGY

	Number of cases	Total number of serum samples tested	Number of cases showing agglutination at 1:16 or higher dilutions	Solid clump at lower dilutions
Bacterial pneumonias	70	78	0	0
Pneumonias of uncertain aetiology	25	49	2*	2

* One of these cases had myeloid leukaemia and the other developed empyema due to an untyped pneumococcus two months after admission to hospital.

There were, therefore, few or no cases comparable to those described by the American authors in this period of the series. One sample of serum from a case in another nearby hospital seen during this period gave a positive test, and during 1945 and 1946 we saw eight clinically typical cases, with titres up to 1:2,048.

Complement fixation with psittacosis antigen

A strain of mouse adapted psittacosis virus, M.O.H. 154, kindly supplied by Prof. S. P. Bedson, F.R.S., was passaged by successive intranasal passage inoculations until 0.05 ml. of mouse lung suspension given intranasally to mice under light ether anaesthesia regularly caused complete pulmonary consolidation and death in three or four days. Smears stained by Machiavello's method at this stage showed many intracellular inclusion bodies. A batch of such infected mouse lungs was ground with 0.9 per cent sodium chloride solution to make a 15 per cent suspension, and the antigen was prepared by centrifugation at 2,000 revolutions and then for an hour at 3,000 revolutions per minute on an angle centrifuge, followed by subsequent heating at 100° C. as described by Bedson (1937). A batch of uninfected lungs was treated exactly similarly, and the resulting preparation was used as a control antigen. The antigens were stored sterile at 4° C. and were checked periodically. All tests were made using psittacosis and a control lung preparation in parallel throughout. This step is important, particularly since it has been reported (Thomas and others, 1943) that in primary atypical pneumonia there commonly appears in the serum the property of fixing complement non-specifically with suspensions of various tissues of small laboratory animals, including mouse lungs. All sera were originally tested within three weeks of being taken and were stored sterile without preservatives at 4° C.

Technique

The usual technique was used. 0.1 ml. of serial twofold dilutions of inactivated serum in 0.9 per cent sodium chloride solutions were allowed to stand at room temperature with 0.1 ml. of diluted guinea-pig serum (equal to 2½ M.H.D. of complement) and 0.1 ml. of psittacosis or normal lung preparations. (These were diluted so as to be equivalent to 7.5 per cent of original lung concentration which had been found optimal by experiments with a known positive serum supplied by Prof. Bedson.) After two hours on the bench, 0.2 ml. of 5 per cent sheep cells sensitized with 5 M.H.D. of haemolytic amboceptor were added, followed by 0.5 ml. of 0.9 per cent salt

solution. Results were read after incubation for 30 minutes at 37° C. and again after the tubes had stood overnight on the bench. The titre was recorded as the serum dilution in the last tube in which no haemolysis had occurred, but when non-specific complement fixation had occurred with the normal lung preparation only those tubes were considered significant which in the corresponding control series showed complete haemolysis.

Results

Tests were performed upon convalescent sera and acute phase sera when available from 35 cases of pneumonia of doubtful aetiology and from 10 cases of pneumococcal pneumonia which showed delay in resolution. Positive results were repeated for confirmation, and in half the cases it was possible to obtain further serum samples as an additional check. Table III shows that some

TABLE III
COMPLEMENT FIXATION WITH PSITTACOSIS ANTIGEN IN THIRTY-FIVE CASES OF PNEUMONIA OF UNCERTAIN AETIOLOGY AND TEN CASES OF PNEUMOCOCCAL PNEUMONIA WITH DELAYED RESOLUTION SELECTED FROM 250 SUCCESSIVE PNEUMONIA ADMISSIONS

	1:2	1:4	1:8	1:16	1:32	1:64
No. of cases with sera giving maximum titre	4	1	3	1*	1	1†

* This was the serum of a ferret convalescent from experimental infection with psittacosis-like virus recovered from Case 2. The patient's serum never fixed complement at a titre greater than 1:2.

† Two acute phase sera from this patient (Case 1) failed to fix complement with psittacosis antigen, but during convalescence the titre rose to 1:64.

degree of complement fixation was found in 11 cases, and that six of these had titres of 1:8 or over, which may be considered significant. None of the patients had any clinical evidence of infection with lymphogranuloma venereum, which is a rare disease among our local population, and it is very unlikely that any of the positive results were attributable to earlier infection with this virus (which is antigenically very similar to psittacosis). On the other hand, since one psittacosis-like virus only was recovered in the whole series we have no definite proof that psittacosis-like viruses had been involved in the others. The evidence, however, is suggestive, especially when taken in conjunction with the finding by Andrewes and Mills (1943) of psittacosis among London pigeons, with Baker's discovery (1942) of a cat-pneumonia virus belonging to the same family which is infectious to man, and with observations in America that up

to 12 per cent of series of atypical pneumonias were probably psittacosis-like in aetiology (Reimann, 1945). Our patients were questioned about associations with domestic birds and animals, but no clues were obtained.

Complement fixation tests with the virus of lymphocytic choriomeningitis

A strain of lymphocytic choriomeningitis (LCM) virus which had been propagated in guinea-pigs was kindly supplied by Dr. F. O. MacCallum, together with some hyperimmune anti-LCM guinea-pig serum. The virus was passaged by intraperitoneal and intracerebral inoculation of spleen material into guinea-pigs until death occurred regularly at seven to nine days. At this stage 10 animals were inoculated and were killed when moribund. Their spleens were ground with five parts of 0.9 per cent salt solution and the resulting suspension was centrifuged on an angle centrifuge for ten minutes at 2,000 revolutions, and then for an hour at 3,500 revolutions per minute. The supernatant fluid was used as test antigen, and was stored at -10°C . A control preparation was made in the same way from normal guinea-pig spleens, and all tests were done with LCM and control preparations in parallel. The antigen prepared in this way was used at a dilution corresponding to 4 per cent original spleen material, and in the same haemolytic system as was used for psittacosis tests it regularly gave complete fixation of complement with a 1:64 dilution of the hyperimmune anti-LCM guinea-pig serum.

Results

Convalescent sera from 22 cases of pneumonia of undetermined aetiology were tested. None of them showed evidence of any complement fixation against LCM, and, since meningitic symptoms were absent from our pneumonia cases, further tests were not made. There was on the whole no evidence to incriminate LCM in our series. In a series of 26 cases in America, Reimann and others (1942) found one case of presumed lymphocytic choriomeningitis, but no series has shown this disease to be an important cause of unusual forms of pneumonia.

Complement fixation with other viruses

When as a result of animal inoculations two virus strains were isolated, one of which proved later to be a mouse pneumonitis virus and the other to resemble psittacosis, attempts were made to detect any possible aetiological role by investigating complement fixation with the sera of the patients who had hitherto been regarded as pos-

sibly ill with a disease of virus aetiology. Mice were infected intranasally with each strain and were killed at three to four days, at which time their lungs were completely consolidated and impression smears showed many inclusion bodies. Since we did not know in which particular fraction of the extracts made from the lungs the possible antigen would be found, the behaviour of the viruses in centrifuged preparation was roughly studied. It was found that infectivity was nearly always associated with the fraction which was deposited during one hour's run at 15,000 revolutions per minute on an Ekko "Blitz" centrifuge, but not during one and a half hours at 3,000 revolutions per minute on an angle centrifuge. Accordingly this fraction, which contained most of the elementary bodies, and the supernatant fluid after centrifuging at 15,000 revolutions per minute, which would contain any soluble antigen which had separated from the elementary bodies, were used in complement fixation tests. In each case the antigen was used in a concentration corresponding to 4 per cent wet weight of lung, and the technique was that described above for psittacosis. Normal lung preparations were used as controls throughout.

Tests were made with 17 sera. None showed any complement fixation with mouse pneumonitis virus preparations. Three sera showed weak complement fixation with the supernatant fluid preparation of virus Sey. Two were sera from patients who also showed good complement fixation with psittacosis antigen, and one was the serum of a ferret which had been experimentally infected with virus Sey and had survived the infection. Five different samples of convalescent serum from the patient Sey were tested, but none showed any convincing complement fixation with this strain, even though it was apparently isolated from her own pleural fluid.

Recent studies by Curnen and Horsfall (1946) on the pneumonia virus of mice (Horsfall and Hahn, 1940) have showed that suspensions of infected lungs would not fix complement with convalescent sera unless the suspensions had first been heated at 80°C . for 10 minutes, and these authors postulate a combination between virus and a tissue component which is infective but would not give serological reactions. If a similar combination occurred with the mouse virus which we studied the negative results which we obtained would not necessarily be significant.

Attempts to isolate virus agents

During the period May, 1943, to October, 1944, 32 samples of material were sent to the National

Institute of Medical Research Laboratories, Mill Hill. The material was from patients who clinically least resembled cases of primary bacterial pneumonia, and from whom no pathogenic organisms had been isolated. In the early part of the series it consisted of small samples of fluid withdrawn by aspiration from the affected parts of the lung, together with pleural fluid when effusion was present, and sputum in some cases. Later in the investigation throat washings and sputum were collected, within the first three days after admission, from all patients the aetiology of whose pneumonia was not obvious. After being kept for, at most, 36 hours in the ice-box, the material was stored at -76°C . until it had been decided whether the case could be diagnosed tentatively as one of primary atypical pneumonia or not, and whether the material should be kept or discarded.

The 32 samples comprised 14 lung puncture fluids, four pleural exudates, three mixed lung puncture and pleural exudates, six mixed lung puncture and sputa, one mixed lung puncture and throat washing, one mixed pleural exudate and throat washing, two mixed lung puncture, pleural exudate, and throat washing, and one mixed lung puncture, sputum, and throat washing.

With one exception, attempts to isolate an agent pathogenic for the species of laboratory animal available were unsuccessful, although in nine instances transient lesions were produced. The results are summarized in Table IV. In some instances, however, pneumonic lesions were produced from which a virus similar to the mouse pneumonitis virus of Nigg (Rake and others, 1942) was recovered.* Substantial evidence was obtained that the virus exists in a latent form in the mouse stock.

Methods

The material was inoculated into mice immediately upon receipt or after storing at -76°C . In

TABLE IV
RESULTS OF INOCULATION OF FILTRATES OF MATERIAL FROM THIRTY-THREE SELECTED CASES OF PNEUMONIA OF UNCERTAIN AETIOLOGY INTO EXPERIMENTAL ANIMALS

No. of cases examined	Positive in mice	Negative in mice but transient reaction in other animals*	Negative in mice and in other animals†
33	1	9	23

* Ferrets, hamsters, voles, and kittens.

† In this column "negative in mice" implies that no agent was isolated which was derived in our opinion from the human patients supplying the material with which they were infected.

most instances ferrets were also inoculated. Administration by the intranasal route under ether anaesthesia was always employed, but in many cases the fluids were also injected directly into the lungs, especially when tissue fluids obtained by lung puncture or pleural fluid were available. In a few instances hamsters, voles, and kittens were also included. Passes were carried out at various intervals after inoculation from the fifth to the fifteenth day.

Isolation of a virus of the ornithosis group

(The clinical details of the patient (Case 2) are given in the Appendix.) A small quantity of blood-tinged fluid obtained by lung puncture and a specimen of pleural fluid were pooled and inoculated intranasally and by direct intrapulmonary injection into two ferrets. When killed 13 days later one of these animals showed a number of haemorrhagic areas in the lungs: further passes in ferrets with a filtrate (0.75 μ gradocol membrane) were negative. On the other hand, the same filtrate contained an agent pathogenic for mice. No lesions appeared in the first group inoculated, but in the second passage one mouse out of six exhibited a small area of consolidation, whilst in the next pass all the mice died with complete pulmonary consolidation. It is curious that the virus was not established by direct passage of the human material in mice.

The lungs of affected mice were rich in elementary bodies readily revealed by the Machiavello method. An attempt to establish the virus by the intracerebral route, using lung filtrate, was not successful until several passes had been made. The virus slowly acquired neurotropic properties and eventually killed mice in five or six days. When injected intraperitoneally, however, the mice remained well, and at necropsy no elementary bodies were found in liver and spleen. Sulphathiazole, sulphadiazine, and sulphapyridine given prophylactically failed to prevent infection. In retrospect this agent shows a marked resemblance to the virus isolated from human patients by Eaton and others (1941) and recently termed pseudopsittacosis by them. A virus of this type has never been detected in the normal ferret and mouse stocks, although it must be pointed out that de Burgh and others (1945) found a spontaneous infection of laboratory mice (exposed to x rays and on a poor diet) with a psittacosis-like agent.

Cases yielding indefinite results

In nine cases, mice inoculated with human material were free from pulmonary lesions, and serial passage of their lungs failed to establish any

agent producing pulmonary consolidation. On the other hand, transient reactions were obtained in other species of laboratory animal, in particular the ferret. Thus, in six out of seven instances ferrets inoculated with the original material showed small areas of congestion and consolidation in the lungs, which were free from bacteria and in which no elementary bodies could be detected. Further passes resulted in the formation of lesions of a similar character (transmission to 2, 2, 3, 3, and 4 generations respectively). No significant increase in the degree of pulmonary involvement was noted, the lesions remaining discrete and involving only a small part of the lungs

(Table V). The results of inoculating mice with the ferret material were consistently negative. It may be noted that Case 10, which produced moderate lesions in the ferret, also caused a reaction of similar type in young kittens, whilst the material from Cases 23 and 25 gave rise to slight reactions in the Orkney vole and the Syrian hamster.

Whether these fleeting reactions can be attributed to a non-specific stimulus provided by the human material or whether an agent of low infectivity was present in the human tissues it is impossible to say. The former hypothesis seems unlikely, since 23 cases failed to provoke any

TABLE V

DETAILS OF ATTEMPTS TO OBTAIN EVIDENCE OF VIRUS AGENTS BY INOCULATION INTO ANIMALS OF MATERIAL FROM CASES OF PNEUMONIA OF UNCERTAIN AETIOLOGY

Case no. and material examined	Ferret	Vole	Hamster	Kitten	Mouse	Complement fixation with psittacosis
2. Sputum and lung puncture ..	±(1) ±(2) +(3) ±(4) +(5)	0	0	0	—(1) —(2) —(3)	—
6. Pleural fluid and lung puncture ..	±(1) —(2)	0	0	0	—(1) —(2) —(3)	—
10. Lung puncture	±(1) ±(2) +(3) —(4)	0	0	±(1) ±(2) ±(3) +(4)	—(1) —(2) —(3) —(4)	—
13. Lung puncture	0	0	0	0	++(1) —(2) —(3)	1:4
14. Lung puncture	++(1) ++(2) —(3) —(4)	0	0	0	—(1) —(2) —(3)	—
17. Throat washings, pleural fluid, and lung puncture	++(1) ±(2) +(3) —(4)	0	0	0	++(1) —(2) —(3) —(4)	—
19. Throat washings, pleural fluid ..	+(1) +(2) —(3)	0	0	0	—(1) —(2) —(3) —(4)	—
23. Throat washings, sputum, and lung puncture	0	+(1) +(2) +(3) ±(4)	+(1) —(2) —(3)	0	—(1) —(2) —(3) —(4)	—
25. Throat washings and sputum ..	—	+(1) +(2) ±(3) —(4)	±(1) —(2)	—(1) —(2)	—(1) —(2) —(3) —(4)	0

(Figures in brackets give the number of the passages. Lesions observed in the lungs are graded from ± = minimal congestion or consolidation in one lobe to ++ = definite discrete areas of consolidation in more than one lobe. — = test negative; 0 = not tested.)

response in the ferret. The second is suggestive, but in view of the indefinite results obtained it cannot be held to have been proved.

Recovery of mouse pneumonitis virus

As mentioned above, the experiments in mice were complicated by the recovery of a virus indistinguishable from mouse pneumonitis virus (Rake and others). In four instances, pulmonary lesions appeared in mice inoculated with the original human material or after one passage. The agent was strictly pneumotropic, since all attempts at provoking infection by routes other than intranasal or intrapulmonary failed completely. Even when large amounts were inoculated intraperitoneally the virus was not recovered from the spleen, and serial intracerebral inoculations were quite negative. Elementary bodies were easily demonstrated in smears from consolidated lungs. Infection was prevented by sulphapyridine, sulphathiazole, and sulphadiazine, but not by sulphanilamide nor by sulphaguanidine.

A virus with identical characteristics was recovered from normal mice taken from the stock used for the above experiments. Some difficulty was experienced, however, in detecting the virus, which presumably exists in a latent or "masked" form. Serial "blind" passes of apparently normal lung tissue through several series of mice at intervals of three or four days, the period which seemed to be the most favourable for the establishment of lung lesions, were completely negative. In three instances, however, pulmonary lesions with elementary bodies were induced after four, five, and five passes respectively when the mice had received a small dose of diphtheria toxin intranasally initially and in the first passage of the series.

Although there is no suggestion that the virus thus isolated is in any way associated with the cause of primary atypical pneumonia, it is interesting that some specimens from human patients were capable of activating the virus.

DISCUSSION

The present survey differs from most others made in this country in recent years in that the net was cast wide, and it includes nearly all the patients who were admitted with pneumonia as their main complaint and who satisfied the criteria laid down—namely, radiographic evidence of consolidation clearing under observation.

In 85 per cent of cases the disease could reasonably be ascribed to accepted pathogenic bacteria. This figure concerns only severe and moderately severe cases in a civilian population, and it is

possible that if a systematic survey of all grades of pneumonia and pneumonitis in the general population were carried out, quite another figure would be obtained. The cases were studied at a time when bold and rational use of sulphonamides by general practitioners had scarcely begun and when penicillin was not yet available. Many of the therapeutic problems, therefore, are of historic interest only, and a comparable series of cases at the same hospital during 1946-7 showed an overall mortality rate of 2 per cent as opposed to 6 per cent. The main unsolved problem in treatment was, and still remains, that of pneumonia in patients with long-standing chronic bronchitis.

A more striking feature of the series is the large number of cases for which no aetiological diagnosis could be made. Even when allowance is made for failure to isolate pneumococci and other pathogenic organisms from the sputum, there remained a group of 15 per cent which were atypical clinically, bacteriologically, and radiologically. Although it seems to be true that in the milder climate and, on the whole, better social conditions which prevail in our district compared with, say, Glasgow or Birmingham, pneumococcal pneumonia is generally a milder disease and less commonly assumes its classical form, there was no evidence that this group consisted really of modified primary pneumococcal pneumonias. At the time we considered that many might be cases of "primary atypical pneumonia," which was coming into prominence particularly among Service men and women in the U.S.A. and in this country. Subsequently to this survey, however, clear-cut cases of this disease have appeared among the local population, and we consider in retrospect that few, if any, were true such cases. The absence of significant cold agglutinins in the sera of all but two patients points to the same conclusion.

Clinically, and probably aetiological also, the group was heterogeneous. One case from which a virus of the psittacosis group was isolated was presumably one of ornithosis. If serological evidence alone can be accepted, a further five cases may have belonged to this group. An incidence of 10 per cent ornithosis in the pneumonias of doubtful primary bacterial aetiology may be compared with the findings of Smadel (1943) of 10 cases in 45 sporadic atypical pneumonias in the eastern U.S.A. and of Meiklejohn and others (1944), who found 10 cases in 250 atypical pneumonias during an epidemic period, also in the U.S.A. A few cases may have been undiagnosed primary staphylococcal or Pfeiffer bacillus pneumonias. One was probably infectious mononucleosis with unusually marked

pulmonary involvement, a condition which has been described by Wechsler and others (1946). Three cases, the case-history of one of whom is given in the appendix, developed transient polyserositis, and were probably due rather to allergy than to a primary infective agent. To the aetiology of the remainder we have no clues, except possibly the transient reactions produced by inoculation into experimental animals. Failure to isolate and maintain a virus pathogenic to laboratory animals is no evidence against human viruses having been present. This fact is amply demonstrated by the successful experimental infection of human volunteers with filtered material from cases of "primary atypical pneumonia of aetiology unknown" (Dingle and others, 1945), despite the failure of many painstaking efforts to infect laboratory animals, and failure to confirm positive results when these were obtained—except for those in cotton rats (Eaton and others, 1944).

It has been shown in experimental animals (see, for example, Harford and others, 1946) that, in the presence of sublethal infection with influenza virus, intranasal inoculation of normally sub-infective doses of pneumococci can give rise to frank pneumonia. There was no evidence in our cases that influenza virus was involved. It is not unreasonable, however, to suppose that other unidentified respiratory virus infections may exist in the community. Mild attacks would be classed as "colds," and the majority would clear up spontaneously and would only be observed during routine radiographs in a chest clinic or in a Services unit, where men receive hospital treatment early and for milder illnesses than civilians. Other attacks, perhaps more severe and treated too lightly, would progress so that secondary bacterial infection supervened in the damaged respiratory epithelium. In this process plugging of small bronchi with mucus and "lobular atelectasis" might play a part (Ramsay and Scadding, 1939). Into this category would fall the considerable number of patients who had an atypical pneumonia with a history of preceding "cold" or "flu," and from whom no normally pathogenic bacteria were recovered. Lastly, attacks might result in an illness severe enough to require proper early treatment in hospital or at home. Such patients would probably automatically receive sulphonamide drugs and nursing attention and, although at first more ill, would escape the effects of secondary bacterial invasion. These would include those patients admitted with high temperatures, suffused faces, and injected conjunctivae, but little or no respiratory distress, who often produced no sputum, and whose illness ran a relatively rapid

course without obvious response to sulphonamides.

It must be emphasized that such an hypothesis is speculative only, and will remain so until a wider range of respiratory viruses has been isolated and until suitable serological methods for obtaining evidence of infection by them have been worked out.

Admission to hospital for pneumonia, as distinct from respiratory morbidity as a whole, appears still to be caused predominantly by the classical bacterial agents.

SUMMARY

1. The clinical findings in 53 cases of pneumonia not attributable to specific bacterial infection are contrasted with those in 298 cases of primary bacterial pneumonia.
2. Complement fixation reactions for psittacosis, lymphocytic choriomeningitis, and mouse pneumonitis were performed in 35 cases. Good serological evidence of infection with the psittacosis group was obtained in three cases, and possible evidence in three more. The other tests were all negative.
3. Only two cases showed significant cold agglutinins, and of these one had leukaemia. It is not thought that "primary atypical pneumonia of aetiology unknown" was involved.
4. Attempts to isolate a virus in animals yielded a virus of the psittacosis group in one case, and transient reactions in animals in nine more.
5. Inoculation of human material was found to activate latent mouse pneumonitis virus in the mouse stock, although this virus had not previously been detected in the stock.
6. The aetiology of the cases is discussed.

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APPENDIX: ILLUSTRATIVE CASE REPORTS

CASE 1: ORNITHOSIS PNEUMONIA (Hospital No. L4556).—A woman aged 29 years was admitted on May 14, 1943, with a history of malaise and feverishness for five days, and of rigor two days before. She had no previous chest history and no history of close contact with animals or birds.

Clinical findings.—She appeared very ill, was cyanosed, and continued to have rigors for four days. Despite this her respiration rate never rose above 24 per minute, and there was no herpes and no pleural involvement. Well-marked consolidation of the right upper lobe cleared in a week, but a similar condition gradually developed in the right mid- and lower lobes, later associated with consolidation in the left mid-zones. She was given 13 g. sulphathiazole and 17 g. sulphapyridine in the first five days, with no improvement. Specific treatment was stopped, and 11 days after admission her general condition began to improve.

Investigations.—In the first two days she brought up a little sputum which contained normal mouth flora only. Afterwards she had no more sputum.

Lung puncture was sterile, and blood culture was twice sterile. White cell counts were done every two

days, and never rose above 15,000 per c.mm. of blood, with normal distribution of cells. There were no cold agglutinins at any stage.

Complement fixation for psittacosis was as follows: second day, none; fourth day, titre 1:2; third week, titre 1:32; sixth week, titre 1:32.

A radiograph of the chest on May 17, 1943, showed consolidation of the lower two-thirds of the right upper lobe (Plate XIVa). By May 21 the right upper lobe was almost clear, and there was consolidation of the right mid-lobe and early consolidation of the left mid-zone (Plate XIVb). By May 24 consolidation extended to the right base, with further consolidation in the left mid-zone (Plate XVa). On May 31 the chest was almost clear, and by July 20 it was clear.

The temperature chart is shown in Fig. 1.

Comment.—This patient gave strong serological evidence of infection with a virus of the ornithosis group, and probably represents the clinical picture of the condition uncomplicated by superimposed bacterial infection (owing to early sulphonamide treatment). We have subsequently (within two years) met four other patients clinically and serologically similar (final titres against psittacosis 1:32–1:128). Failure to isolate a causative agent by animal inoculation is easily attributable to the paucity of material, obtained by lung puncture, which was sent to Mr. Glover.

CASE 2: ORNITHOSIS PNEUMONIA (Hospital No. L5104).—A woman aged 27 years was admitted on May 16, 1943, with a history of malaise, feverishness, right-sided pleural pain, and frequent vomiting, beginning seventeen days before. She had received 35 g. sulphapyridine before admission, and when seen she was moderately ill with temperature 104° F., pulse rate 110 per minute, and respiration 28 per minute. There were indefinite signs of consolidation in the right mid-lobe, with some fluid posteriorly. These physical signs were still present when she was discharged from hospital seven weeks later, although her clinical condition had improved gradually.

FIG. 1.—Case 1.

FIG. 2.—Case 2.

Investigations.—Although she had produced a little yellow sputum before admission to hospital, she produced none after. Faintly turbid straw-coloured fluid (100 ml.) was aspirated from the pleura on the day of admission. It was sterile on culture and did not produce tuberculosis in a guinea-pig. Lung puncture was performed at the same time and was combined with pleural fluid for animal inoculation by Mr. Glover. A virus of ornithosis group was isolated.

The Mantoux reaction was faintly positive to 1:1,000 old tuberculin. White cell counts on the second, fifth, and ninth days after admission ranged between 3,800 and 4,500 per c.mm. of blood. Cold agglutinins were absent on three occasions. Convalescent serum gave weak (1:2) fixation with psittacosis antigen. No complement fixation was obtained with the ornithosis virus isolated from this case.

On admission a radiograph of the chest showed consolidation of the right mid-lobe with loculated fluid posteriorly. One month later the consolidation was clearing but the fluid remained (Plate XVb). Four months later there was continued slow clearing of consolidation and fluid, and eleven months later the lung was practically clear.

The temperature chart is shown in Fig. 2.

Comment.—The isolation of a virus of the ornithosis group has been described in the text. Despite absence of serological confirmation, this patient probably had a clinical infection with this virus.

CASE 3: ? INFECTIVE MONONUCLEOSIS (Hospital No. M 2517).—A woman aged 26 years was admitted on Mar. 7, 1944, with a history of

headache, backache, and dry cough for 10 days, and a sore throat with swollen cervical glands for five days. She had no previous history of chest disease.

Clinical findings.—There were small ulcers, 2 mm. in diameter, on her tonsils and pharynx, which gradually spread during the next 12 days to involve the soft palate and the floor of her mouth. Palpable tender glands were present in both posterior triangles of her neck. Both bases showed persistent rales, which appeared to be clearing up until the tenth day after admission, when a rise in temperature was accompanied by an increase in signs at the left base. Her condition gradually improved during the course of three weeks, during which she received no specific treatment.

Investigations.—No pathogens were isolated from sputum or throat swabs on three occasions.

White cell counts were as follows: first day after admission, 18,000 per c.mm. of blood (65 per cent lymphocytes); sixth day, 11,000 per c.mm. (76 per cent lymphocytes); tenth day, 6,000 per c.mm. (64 per cent lymphocytes); twenty-first day, 4,500 per c.mm. (61 per cent lymphocytes).

Blood culture was sterile on two occasions.

A Paul-Bunnell test on the first day after admission gave a titre of 1:32; on the ninth day it was 1:16. Cold agglutinins were absent from acute and convalescent sera. Complement fixation with psittacosis antigen was negative.

A radiograph of the chest taken on admission showed mottled consolidation of both lower lobes, more on the right than on the left (Plate XVIa). Two weeks later there was partial clearing (Plate XVIb), and four weeks later the chest was clear.

The temperature chart is shown in Fig. 3.

Comment.—From this case (No. 23, Table V) throat washings, sputum, and lung puncture material gave rise to transient reactions in voles and hamsters. The general clinical picture fitted a diagnosis of glandular fever with associated pneumonia, as has been later described by Wechsler and others (1946), but no confirmation was provided by the Paul-Bunnell test.

FIG. 3.—Case 3.

PLATE XIV.—*Case 1* (ornithosis pneumonia). (a) Ninth day of the disease. (b) Thirteenth day of the disease.

(b)

(a)

PLATE XV.—(a) *Case 1*. Sixteenth day of the disease. (b) *Case 2* ornithosis pneumonia). Thirty-fourth day of the disease.

PLATE XVI.—Case 3 (glandular fever). (a) Thirteenth day of the disease. (b) Twenty-fifth day of the disease.

PLATE XVII.—*Case 4* (aetiology undetermined). (a) Tenth day of acute disease.
(b) Twenty-fourth day of acute disease.

PLATE XVIII.—Case 5 (aetiology undetermined). (a) Antero-posterior, and (b) lateral views taken on the tenth day of the disease. (c) Twenty-first day of the disease.

PLATE XIX.—*Case 6* (pulmonary infiltration with eosinophilia). (a) Third week of the disease. (b) Seventh week of the disease.

FIG. 4.—Case 4. Day after admission

CASE 4: UNDETERMINED AETIOLOGY (Hospital No. M 3073).—A fitter aged 58 years was admitted on April 25, 1944, with a history of having been away from work for one month because of a severe "cold" and cough, with general malaise and pains in his chest and all joints. One week before admission there was recurrence of pain in his joints and in the right side of his chest, and he became generally prostrate. He had no previous chest history.

Clinical findings.—He was distressed and ill, with moderate dyspnoea. There were signs of consolidation in the lower lobes of both lungs. The joints of his hands and feet were swollen and red (this condition subsided upon treatment with sodium salicylate 120 gr. (8 g.) daily for twelve days). His general condition did not improve in hospital, and consolidation increased until the lower two-thirds of both lungs were involved: 20 g. sulphamezathine and 40 g. sulphathiazole had no effect upon his temperature or his condition. His blood urea was not raised. He died after eighteen days. Autopsy was refused, but material for culture was aspirated through a wide needle from both lungs within four hours of death.

Investigations.—Very little sputum was produced. This grew commensals with moderate growth of *H. influenzae*. There were no tubercle bacilli in films. Lung puncture was performed at necropsy. Culture was sterile. Animal inoculation gave rise to mouse pneumonitis virus. Blood culture was sterile.

On the first day after admission the white cell count was 13,000 per c.mm. of blood (72 per cent polymorphs, 5 per cent monocytes). On the twelfth day it was 17,500 per c.mm. (74 per cent polymorphs,

10 per cent monocytes). On the sixteenth day it was 31,000 per c.mm. (85 per cent polymorphs, 5 per cent monocytes).

Cold agglutinins were absent throughout, and complement fixation with psittacosis gave negative results.

Four days after admission a chest radiograph showed irregular consolidation of the right mid-zone and right and left bases (Plate XVIIa). Another radiograph thirteen days after admission showed increase in consolidation with extension to left mid-zone. Seventeen days after admission consolidation had become confluent (Plate XVIIb).

The temperature chart is shown in Fig. 4.

Comment.—The mouse pneumonitis virus isolated from animals inoculated with lung puncture material was almost certainly a contaminant strain. Although *H. influenzae* may have contributed to his death, we inclined to assign some other unidentified cause to the pneumonia.

CASE 5: UNDETERMINED AETIOLOGY (Hospital No. L 3850).—A woman aged 52 years was admitted on April 6, 1943, with a history of sore throat and swollen neck glands a fortnight previously. The condition subsided after three days, but one week before admission she felt feverish, with pain in the left side of her chest and nausea. She said that she was jaundiced, and that she had twice before been jaundiced during the previous twenty years. No jaundice was evident on admission. There was no history of previous chest disease.

Clinical findings.—She was an ill woman with a painful cough which produced little sputum. There were signs of consolidation at the left base, and signs suggesting a cavity near the eighth dorsal vertebra. A course of 36 g. sulphathiazole in the first seven days did not affect her condition, which improved slowly over a period of four weeks.

Investigations.—On the day of admission, and eight days later, the sputum yielded normal flora only. Lung puncture was performed ten days after admission. Culture was sterile. Blood culture was sterile on admission.

The white cell counts were: second day after admission, 8,300 per c.mm. of blood (80 per cent polymorphs); sixth day, 12,900 per c.mm. (72 per cent

FIG. 5.—Case 5.

polymorphs); eighth day, 5,600 per c.mm. (74 per cent polymorphs); twenty-first day, 6,500 per c.mm. of blood (60 per cent polymorphs).

A radiograph of the chest taken on the second day after admission showed fine mottled consolidation of the left lower lobe (Plates XVIIIa and b). On the seventh day after admission there was no change, but by the thirteenth day there was partial clearing (Plate XVIIIc). On the twenty-second day a bronchogram showed no evidence of collapse or other abnormality in the left lower lobe.

The temperature chart is shown in Fig. 5.

Comment.—Complement fixation tests with psittacosis and lymphocytic choriomeningitis antigens were negative, and cold agglutinins were absent. At the time, inoculation into animals in order to recover virus had not been begun, and evidence on this point is lacking. It is possible that the patient had pneumonia surrounding an embolic lung abscess, but there was no definite evidence for this, and the aetiology remains obscure.

CASE 6: PULMONARY INFILTRATION WITH EOSINOPHILIA (Hospital No. P4160).—A woman aged 46 years was admitted on March 23, 1944, with a history of cough and left pleural pain for seven days and right pleural pain for five days. She gave an indefinite history of mild asthmatic attacks.

Clinical findings.—She was cyanosed and ill. There were signs of consolidation and fluid at both bases, and she had herpes labialis. She was given 43 g. sulphamezathine with no improvement in her condition, and continued ill for four weeks. During this period pale yellow opalescent pleural fluid was aspirated from both sides on several occasions. After three weeks pericardial friction was detected, and she developed small pericardial effusion and just detectable ascites. After seven weeks her temperature rose again, and remained around 100° F. for three weeks, although she did not feel ill. There was still fluid at both bases and some underlying consolidation. During this febrile period she had transient eosinophilia (20 per cent) lasting for two weeks. In view of the eosinophilia she was given intravenous neoarsphenamine, which resulted in an immediate rise of temperature to 103° F. and arsenical dermatitis. The dermatitis subsided when treatment was discontinued, and during the next two weeks there was gradual improvement in all symptoms, with settling of temperature to normal. Eighteen weeks after admission she had a further rise of temperature to 100° F., and a small

right pleural effusion was detected, but she was clinically well and there was no underlying pulmonary infiltration.

Laboratory investigations.—A little sputum was produced during the first week; it contained no pathogenic organisms.

Pleural fluid was found to be sterile on several occasions. Cells were mainly lymphocytes (eosinophils never more than 2 per cent). Guinea-pig inoculations were negative for tubercle bacilli.

Gastric lavage was negative for tubercle bacilli. Blood cultures were four times sterile. The Wassermann reaction was negative. Blood agglutination against salmonella and brucella was negative. Cold agglutinins were absent. The complement fixation test with psittacosis was negative.

The white cell counts were: three days after admission, 16,000 per c.mm. of blood; two weeks after admission, 11,000 per c.mm.; three weeks after admission, 8,700 per c.mm.; seven weeks after admission, 12,000 per c.mm. (20 per cent eosinophils); eight weeks after admission, 10,000 per c.mm. (20 per cent eosinophils); ten weeks after admission, 6,000 per c.mm.; sixteen weeks after admission, 5,000 per c.mm.

A radiograph of the chest taken on admission showed consolidation of both bases with fluid. Two weeks after admission there was fluid at both bases, at the left more than the right (Plate XIXa). Three weeks after admission there was possible pericardial effusion. Six weeks after admission the right base was clearing, but there was still fluid at the left base (Plate XIXb). Nine weeks after admission there was no change. Thirteen weeks after admission the radiograph was clear.

The temperature chart is shown in Fig. 6.

Comment.—This case was admitted primarily as one of pneumonia, but the patient developed polyserositis and swollen joints. She was considered to have either some obscure respiratory virus infection, or possibly some condition related to Wiengarten's (1943) "tropical eosinophilia," or even periarteritis nodosa. No virus was isolated, and the subsidence of symptoms following treatment with arsenic suggests that the second diagnosis may have been correct. No mites were seen in the scanty sputum samples examined.

Two years later this patient developed increasing ascites and evidence of hepatic disease. She died on June 11, 1947, when the coroner's post-mortem examination revealed a lobular cirrhosis of the liver, causing severe haemorrhage from oesophageal varices. There were no gross lung changes.

FIG. 6.—Case 6.