Acta Medica Scandinavica. Vol. CXXX, fasc. III, 1948.

From the State Bacteriologic Laboratory, Stockholm.

Primary Atypical Pneumonia.

A Report of 112 Cases with a positive Cold Agglutination Reaction.

By

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(Submitted for publication August 4, 1947.)

Introduction.

Primary atypical pneumonia is an acute infectious disease in the respiratory tract. It has been especially studied in U. S. A. and England during the past few years. There is, however, no reason for assuming that it is a new disease; it has without doubt existed for many years in other countries also, among them Europe. As far back as 1918, Clough and Richter (6) described a couple of typical cases, and in 1935 a fairly large epidemic was reported by Bowen (3) from a military camp at Hawai. A fairly extensive epidemic was also described by Reimann in 1938 (22). In England, the disease was observed by Scadding and Ramsay (25, 26) in 1937. The first fairly exhaustive description of it was furnished by Kneeland and Smetana (17) and by Longcope (18), in 1940. During the War, it was very common among soldiers both on active service and in training camps, and in connection with these epidemics a number of publications have appeared giving detailed reports both on the clinical picture and the etiology of the disease (2, 8, 9, 10, 11, 12, 19, 21, 23, 24, 31, 32, 33, 34, 35).

In Scandinavia, the disease was first mentioned in Sweden in the spring of 1945 (15), and since then several authors have published papers on it, from Denmark, among other countries

(1, 16, 27, 28, 29, 30). The disease has previously been known under a variety of different names, such as interstitial pneumonia, pneumonitis, virus pneumonia, and others. The name now generally accepted in U. S. A. is primary atypical pneumonia. The term often used in Sweden, virus pneumonia, cannot be regarded as adequate, as, in the first place, the disease is presumably caused by several different infecting agents, and in the second place, none of these has yet been demonstrated with certainty. According to Horsfall (14), it is also possible that the disease is due to a synergy between virus and bacteria, a so-called complex infection.

Judging by earlier American investigations the opinion held was that the disease constituted, from the clinical aspect, a relatively uniform group, but in later publications an ever increasing number of authors are abandoning this view. In one of the latest articles, for instance, the Commission of Acute Respiratory Disease (4) asserts that »atypical pneumonia may be one disease or it may be several diseases; it may be produced by one agent or by many agents; it may have only one clinical form or it may vary from the mildest of infections of the upper respiratory tract to the most severe and fatal pneumonia; it may spread only by direct and intimate contact with cases and carriers, or it may be air-borne in the truest sense».

Material.

My material consisted of patients with suspected primary atypical pneumonia from whom blood samples for the estimating of cold agglutinins had been sent to the State Bacteriologic Laboratory. In 112 cases the reaction was positive and only these cases were included in the present investigation, as the object was to obtain as homogeneous a material as possible. This does not mean, however, that clinically typical cases with a negative reaction could not have been primary atypical pneumonia. The cold agglutination test was considered positive when, from having been negative in serum taken during the acute phase of the disease, it was positive in the convalescent stage with a titer of at least 1/8—1/16. The same was the case if the titer increased during the course of the disease from, for instance 1/4 to 1/16. A single value from the convalescent phase of the disease, with a titer of at least 1/16, was also considered to be sufficient. In American investigations, a borderline titer of 1/16 is often stated to be

too low. This value was regarded as sufficient in the present investigation, however, since with the method used, only a few sera had a titer of 1/16 or over among a total of 500, consisting of both normal sera and sera from patients with infections of the upper respiratory tract of a different origin.

Methods.

Sputum. The sputum samples examined were kept in a frozen state at — 70° C. In the examinations for virus, sputum samples were obtained during the acute stage of the disease and were frozen as soon as possible, as a rule not later than a couple of hours after they had been obtained. Pulmonary tissue from the only patient who died was also preserved in the same way.

Culture medium. In the examination of the ordinary throat flora a blood agar plate with 10 per cent blood was used. This was incubated in a thermostat for 24 hours at 37° C. and analyzed for α-streptococci, β-streptococci, staphylococcus albus and staphylococcus aureus. In tests for the purpose of demonstrating a specific encapsulated gamma streptococcus the selective medium described by Horsfall et al. (7, 20) was used.

Virus. Sputum samples were ground together with fine sand and broth and were then centrifuged for 10 minutes at 1,500 R. P. M. The only piece of pulmonary tissue examined was treated in the same way. The supernatant fluid obtained after the centrifuging was used for inoculation. Mice and guinea-pigs were used as the experimental animals. These were inoculated intranasally, intracerebrally and intraperitoneally. The animals were killed 7—14 days after the inoculation and submitted to examination. Serial passages were done with a 20 per cent lung suspension from the animals that had been inoculated intranasally.

Cold agglutinins. Wherever possible, blood samples were taken during the first days of illness and again after about 10 days, or during the convalescence. The blood was kept at room temperature until the serum had been separated by centrifugation.

Human 0 red cells which had been washed twice with physiologic saline were used as antigen in a 1 per cent red cell suspension.

0.3 ml of red cell suspension was added to 0.3 ml of a falling series of serum dilutions (1/2, 1/4, and so on). The dilutions were prepared in physiologic saline, and ordinary Widal tubes were used for the titrations. Readings were made after the tubes had been kept overnight at a temperature of + 5° C; the readings had to be done immediately after the samples had been brought from the cold-room as the agglutinins become rapidly eluted when kept at a higher temperature. The results were recorded by the same method as that used in Paul-Bunnell's reaction. The reaction is considered as strongly positive (5 plus) when a solid disk which can be shaken up as a firm flake and the positive reactions are then graded according to the durability of the flake in the following manner.

5 plus: The flake can be shaken without falling to pieces.
4 plus: The flake breaks up into large fragments.
3 plus: The flake breaks up into small fragments readily distinguishable with the naked eye.
2 plus: The flake breaks up into small fragments which are just distinguishable with the naked eye.
1 plus: The flake breaks up into very fine fragments which are distinguishable under a magnifying glass. This is counted as a negative reaction.

In the positive samples, the 5 plus reaction often occurs high up in the dilution series while it hardly occurs at all in normal sera, even in the lowest dilutions. The reaction was checked by placing the positive tubes in a thermostat at + 37° C for half an hour and then taking another reading. No agglutination should then be found.

Clinical Laboratory Findings.

White blood cells and sedimentation rate. A white cell count and a sedimentation rate according to Westergren, were carried out in every case. The highest white cell counts are shown in table 1.

Table 1.

The highest total white blood cell counts in 112 cases of primary atypical pneumonia.

White blood cells per ml	No. of patients in given range
3,000— 6,000	21
6,000— 9,000	40
9,000—12,000	28
12,000—15,000	10
15,000—20,000	10
> 20,000	3

In 89 cases the white cell count was normal or only moderately raised during the whole illness. In a few cases, however, especially in patients with a moderately severe or severe form of the disease, a high white cell count was obtained. A feature of interest was that the white cell count often only reached its highest level towards the end of the febrile period. The sedimentation rate was considerably increased in most of the cases, and values of over 100 mm in 1 hour were a not uncommon finding.

Bacteriologic studies. Cultures from sputum made on ordinary blood agar plate yielded a rather various flora of bacteria, the

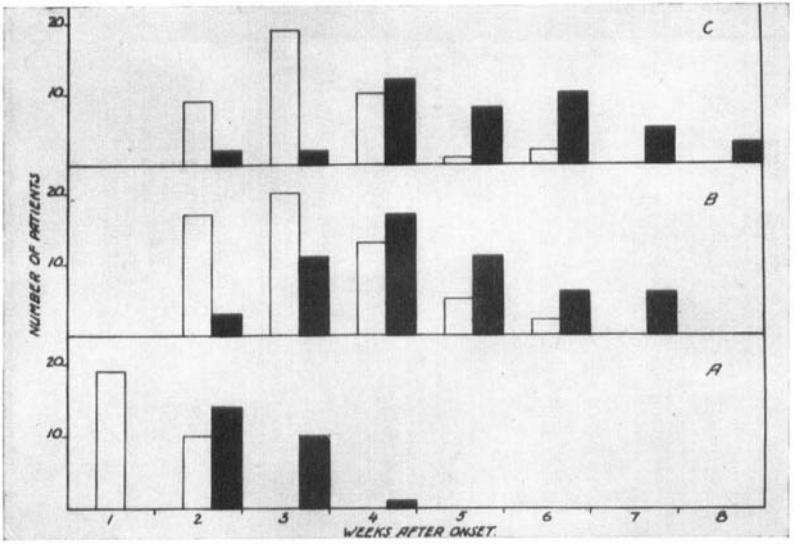

Fig. 1. Time of appearance and disappearance of cold agglutinins in Primary Atypical Pneumonia.

A. First appearance (29 cases): open bars last negative test; solid bars = first positive test.

B. First significant (2 fold or greater) drop in titer (55 cases); open bars = last observation of the maximum titer; solid bars = first test after the drop in titer.

C. Disappearance (41 cases): open bars = last test before a 2 fold or greater drop in titer to 16 or less; solid bars = first test in which the titer was 16 or less (the last of these includes 1 case each on days 56, 63 and 98 respectively).

predominating type being α-streptococci. On the whole, the same bacterial flora was obtained as in healthy individuals. At the clinics where examinations for pneumococci were routinely made, several types, especially those of the higher types, were demonstrated in a number of cases. These do not seem to have played any part in the course of the disease, however.

When Horsfall's special medium was used, an encapsulated streptococcus resembling the MG-streptococcus found by American investigators was demonstrated in only one case.

Virus studies. Attempts were made to detect virus in a few cases. So far, however, all these experiments have had a negative result. In some instances, latent virus types in the experimental animals made it impossible to judge the results. We have not yet performed any tests by the Eaton method, by which preliminary inoculation of the amniotic sec in chick embryos, followed by passage of amniotic fluid to cotton rats, is done.

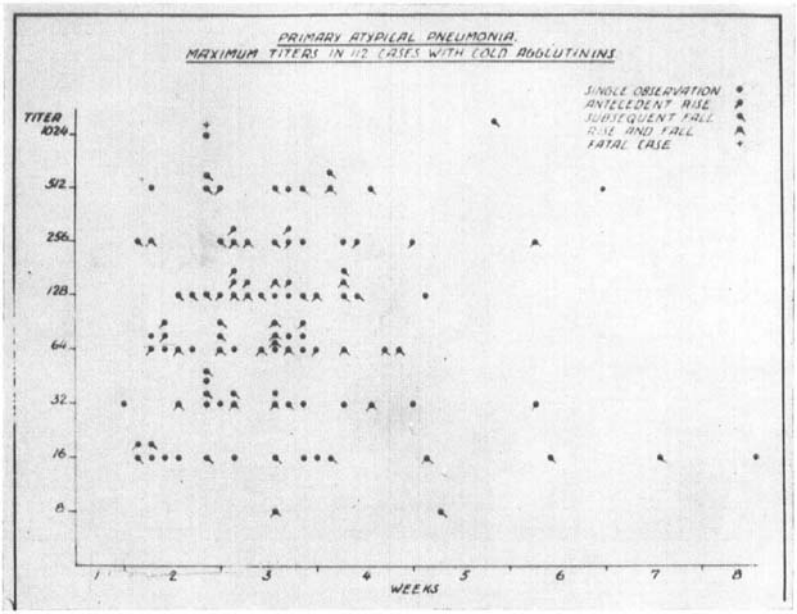

Fig. 2. Each dot represents the maximum titer of cold agglutinins in one patient and the time after the onset of the disease when that titer was first demonstrated. A short line sloping up to a dot from the left indicates that observations of lower titers were made in that case before the maximum titer was obtained. A similar line sloping down to the right from the dot indicates that there were subsequent observations of lower titers. Dots without such lines indicate single observations or multiple observations of the same titer within a brief period.

Serologic studies. Sera from patients taken both during the acute stage and during convalescence were tested by slide agglutination against the encapsulated *a*-streptococcus that was found, Agglutinins in low titer were demonstrated in about the same proportions in acute phase and in convalescent serum, and this streptococcus could therefore not be used for purposes of diagnosis.

In all the cases included in this study cold agglutinins, as mentioned before, were demonstrated in the serum. During the course of the illness, the earliest positive sample (fig. 1 A) was obtained between the 8th and the 28th day and the large majority were obtained during the second or third week. The last negative sample was obtained from the same cases during the first or second week. The highest titer (fig. 2), was found in most cases between the 10th and 28th day. In a few cases, however, the highest titer was registered as late as the 5th to 6th week, and in a few

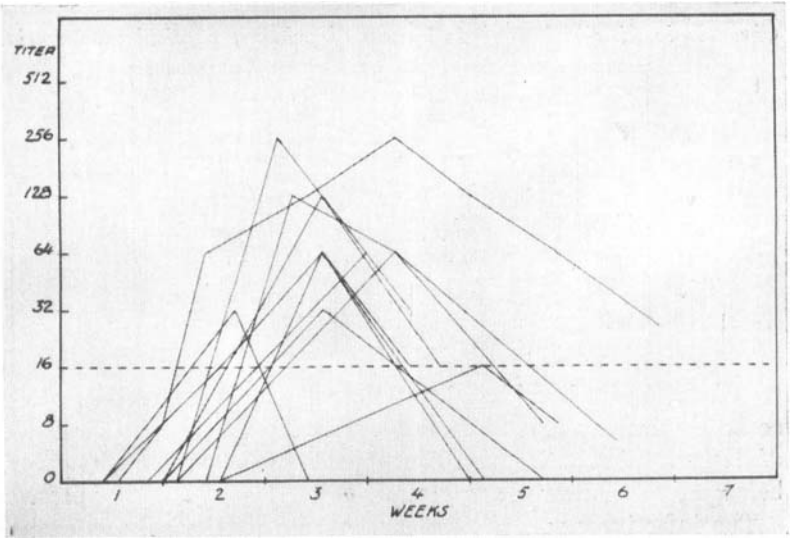

Fig. 3. Titers of cold agglutinins in a few representative cases.

cases between the 7th and 10th day. The first significant drop in the titer occurred between the 3rd and 5th week (fig. 1 B) and a titer of less than 1/16 was found in most cases after the 4th to 7th week (fig. 1 C). In a few isolated cases posivtie samples were obtained for as long a period as 2 months.

Figure 3 shows the course of the cold agglutination in a few representative cases. In those cases where the reaction never reaches high titers there is the risk that the point of time when a sure positive titer can be obtained will be missed if samples are not taken repeatedly at relatively short intervals.

Clinical Findings.

Epidemiology. The investigation included cases that occurred between May 21, 1945 and Oct. 1, 1946. The number of cases occurring in the different seasons of the year are shown in table 2.

During the first period, January to March 1945, only a few samples were sent in. More than 50 per cent of the cases occurred during October 1945 and between the months of January and March, 1946. This distribution of the cases indicates that the disease may be seasonal in type, with the majority of the cases concen-

Table 2.

Chronologic distribution of 112 cases of primary atypical pneumonia.

	Month	No. of cases within given range of months
1945	Jan. —March	5
	April—June	4
	July —Sept.	17
	Oct. —Dec.	37
1946	Jan. —March	24
	April—June	12
	July —Sept.	13

trated to the darkest months of the year as is the case in other acute respiratory tract infections. The disease attacked people of all ages and of both sexes. The majority of the patients, however, belonged to the lower age groups, below the age of 30 years.

The infectivity was not serious, and no particularly extensive epidemics occurred. On a couple of occasions, however, an epidemic spread was observable, both in a couple of families and among the children in a school. The latter epidemic has been described by Jonsson (16) from the Norrtull Children's Hospital. Another exception was that a number of nosocomial infections occurred; at Ersta Hospital, for instance, there was a small epidemic, with an Estonian refugee as the primary source of infection. The path of infection in this case was direct and intimate contact with the person affected, and there was in all probability no question of an air-borne infection.

Onset of the disease. In the present material, the onset was insidious in 53 per cent of the cases while in 47 per cent it was more acute. In those cases where the onset was insidious the commonest symptoms were weariness and general malaise. Coryza, cough, nausea and headache were also experienced by these patients. In cases where the onset was more acute the malaise was more pronounced and chills occurred in many cases. Pains in the muscles, generalized aches, and a sharp pain in the chest were also common symptoms. In many of these cases, it was impossible to distinguish the acute stage from influenza or pneumococcal pneumonia. As a rule, the general condition remained relatively unaffected in spite of the fact that the onset had been acute.

Symptoms during the course. The symptoms most commonly occurring during the patients' illness are shown in table 3.

Table 8.

Symptoms in 112 patients with primary atypical pneumonia.

Symptoms		Patients	
		Number	Per cent
General:	Headache	34	30
	Malaise	40	36
	Chills or chilliness	41	37
	Generalized aches	7	6
	Anorexia	10	9
	Nausea	4	3.8
	Vomiting	2	1.8
Respiratory:	Cough	101	90
	Sputum	40	36
	Bloody sputum	8	7.4
	Sore throat	9	8
	Chest pain	26	23
	Epistaxis	5	4.5
	Dyspnoea	7	6

Cough. Cough was the commonest symptom; in many cases it was the only noticeable one except fever. It was a hard, dry, irritative cough, which became looser, with mucoid or mucopurulent sputum, during the later part of the illness. The sputum was in some instances blood-streaked or blood-tinged. In many cases the amount of sputum was small during the entire course. The cough persisted, as a rule, during the febrile stage, in some cases long after the temperature had returned to normal, and was in many cases very troublesome.

Pains. Substernal pain, as well as pleural pain, was present in many cases. In a couple of patients these pains were focussed in the abdomen, and one patient was sent to the hospital on a diagnosis of acute abdominal disorder.

General condition. More than one-third of the patients experienced a certain degree of malaise, but on the whole the general condition, in all except the more serious cases, was unaffected.

Chills. Chills were experienced by about 40 per cent of the patients but in most instances they were mild. Fits of ague were rare.

Headache. Headache, which is stated in the American literature to be a very typical and common symptom, was only present in 30 per cent of my cases. As a rule it was mild and uncharacteristic.

Physical Signs.

The physical signs have been assembled in table 4.

Table 4.

Abnormal physical signs in 112 patients with primary atypical pneumonia.

Physical signs	Patients	
	Number	Per cent.
Fever	109	98
Nasal Congestion	11	10
Pharyngitis	71	63
Pulmonary signs	90	80
Dulness	42	37
Râles	82	73
Tachycardia	4	3.5
Cyanosis	9	8

Fever. Of the 83 patients whose temperature curve could be followed from the onset, 41 had a temperature of 39° C. or over during the first day. During the remainder of the course the fever was remittent; a continuous high fever or intermittent fever was uncommon. The drop in the temperature was generally lytic, a critical temperature drop being very rarely observed. The average number of days with fever was 12—15, varying between 4—6 days and up to 50 days.

Tachycardia and cyanosis were uncommon findings, and *herpes labialis* was only encountered in one patient.

Pharyngitis and rhinitis. Pharyngitis was present in 63 per cent and rhinitis in 10 per cent of the cases, usually in a mild form.

Lungs. The physical signs from the lungs were as a rule less pronounced than those found in lobar pneumonia. The most characteristic finding was diffuse râles, these occurring in 73 per cent of the patients. In only one-third of the cases was dulness established. The physical examination yielded a negative result in 20 per cent of the cases.

Course. The course of the disease showed considerable variation in the different cases. Only one death occurred. The other patients all recovered. The total time of illness, from the onset to the day when the patient was discharged, will be seen in figure 4.

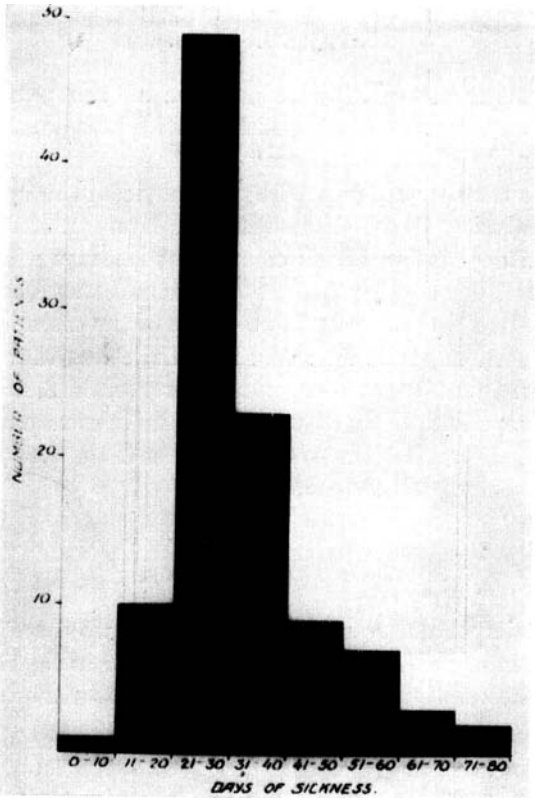

Fig. 4. Duration of sickness in 112 cases of Primary Atypical Pneumonia.

The majority of the patients were ill for 21—30 days and a relatively large number for 31—40 days. The disease in most cases took a much longer course than the course usually observed in lobar pneumonia.

Complications. Complications were rare. Acute sinusitis and otitis occurred in a couple of patients.

Chemotherapy, including penicillin. No very thorough attempt to judge the therapeutic value of sulfonamides and penicillin was made. Most of the patients were given sulfonamides in various dosages. Penicillin was, as a rule, given only at the hospital, and in these cases the treatment was carried out more consistently. No unequivocal results as regards the effectiveness of sulfonamides or penicillin were obtained.

X-ray Findings.

X-ray films of the lungs were taken in all cases, and in most instances they were also submitted to control examinations during the course of the illness. The X-ray showed, as a rule, more extensive changes than were indicated by the physical findings. A more detailed analysis will be furnished in a later publication. (36). Only a brief description of the commonest findings will therefore be given here. Usually, the pneumonic process was located in the lower lobes. In a little less than two-thirds of the cases the changes were present in one lobe only and in a little less than one-third in two lobes. In a few cases they were observed in 3, 4 or 5 lobes. Changes observable on the X-ray films were in most cases already present 1—2 days after the onset, and in a little over two-thirds of the cases they persisted for 3 weeks.

Two Typical Cases.

The most important results obtained from two cases[1] that could be followed in some detail have been assembled in figures 5 and 6, and a short description of the course of the illness will be given here.

Case 1. (Fig. 5.) A 45 year old business man became acutely ill, with malaise and a temperature of 40 degrees. Two days later he was admitted to the hospital. His general condition was then affected, he had

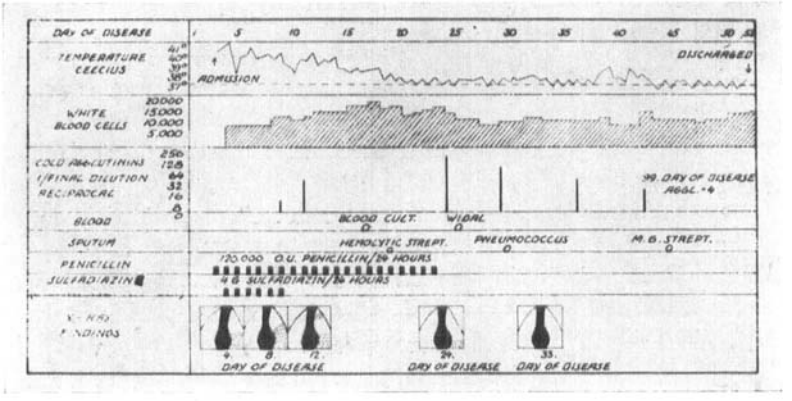

Fig. 5. Relevant findings and Therapy in a characteristic case of severe Primary Atypical Pneumonia.

[1] These two cases have kindly been placed at my disposal by Dr. A. R. Frisk.

high fever (41° C) and a severe cough with a little sputum. No cyanosis or dyspnoea. Râles were heard over the base of the right lung. He was treated with sulfapyrimidine and penicillin but without success. His temperature was around 39°—40° C for 12 days, and only after some time did it begin to fall gradually. During the first few weeks his general condition was strongly affected and he had auricular fibrillation for a time. The extent of the pneumonic process will be seen in figure 9. His cough became loose after a time with copious sputum. Cystopyelitis due to streptococcus faecalis, developed during the subsequent course. The diagnosis, primary atypical pneumonia, was confirmed by a positive cold agglutination test, which became positive about 8 days after the onset and reached its maximum at the end of the febrile period. The patient's general condition improved very slowly, and for a long time after his discharge he was convalescent; only after $2^1/_2$ months from the onset of the disease was he able to work at his full capacity.

Case 2. (Fig. 6.) A woman, aged 42, fell acutely ill with a temperature of 39.1° C, a dry cough, and a severe headache. Three days later sulfapyrimidine was administered but had to be withdrawn after one day because of severe vomiting. Five days after the onset the patient was admitted to the hospital. Her general condition was then relatively unaffected, but she complained of a severe headache and was troubled by a dry cough. The extent of the pneumonic process will be seen from figure 6. Penicillin therapy was tried but it had no effect. The tempera-

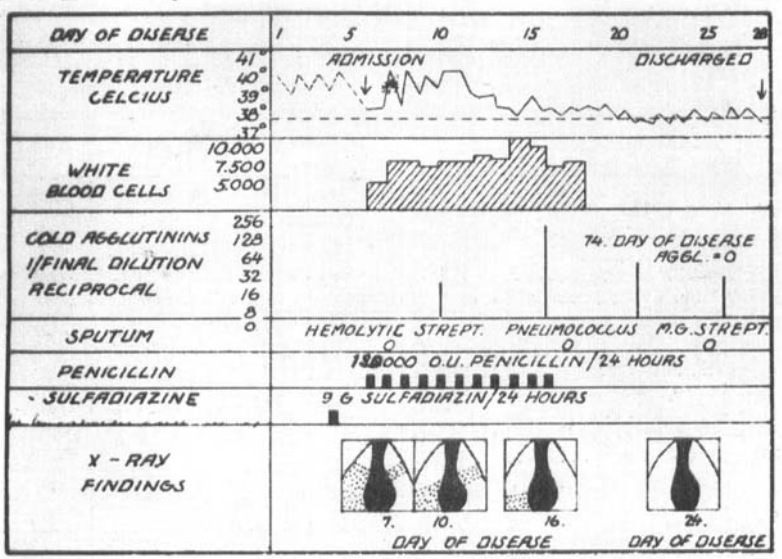

Fig. 6. Relevant findings and therapy in a characteristic case of Primary Atypical Pneumonia of Moderate Severity.

ture remained for another week around 38°—40° C and then began to show a lytic fall. The dry cough, which was one of the most troublesome symptoms, became looser in the later course of the illness. The diagnosis, primary atypical pneumonia, was confirmed by a positive cold agglutination test which in this case was demonstrated about 8 days after the onset and reached the highest titer at the close of the febrile period. After the temperature had returned to normal the patient rapidly improved, and about 3 weeks after the onset of the disease she was almost completely restored to health.

Factors Influencing the Cold Agglutination Titer.

In a number of American publications (5, 13) it is stated that the height of the cold agglutination titer is related to the severity of the disease, in other words, the higher the titer the more severe is the course of the disease, and vice versa. In order to ascertain whether similar conclusions could be reached with regard to my material, the highest cold agglutination titer obtained was compared with some of the symptoms that could be followed most closely. These were, first, the highest temperature lasting at least 24 hours that could be observed; second, the number of days the fever lasted; and third, the highest number of white cells occurring during the course of the disease. The results have been assembled in table 5.

Table 5.

Relation of maximum cold agglutinin titer in 97 cases to the height and duration of fever and to the leukocyte count.

Maximum titer	>16	16—32	64—128	256—512	Total
Maximum temperature					
Less than 38° C		1		1	2
38°—39°		4	2	2	8
39°—40°	1	15	29	12	57
40° or higher		4	15	11	31
Totals	1	24	46	26	97
Duration of fever					
7 days or less	1	7	2		10
8—14 days		11	22	3	36
15—21 days		5	15	17	37
22 days or more		1	7	6	14
Totals	1	24	46	26	97
Leukocyte count					
Less than 7,500	1	12	12	5	30
7,500—12,500		7	25	13	45
12,600 or more		5	9	8	22
Totals	1	24	46	26	97

It will be seen from the table that the height of the fever is not in direct relation to the cold agglutination titer. The distribution around the commonest titer of 1/128 is fairly even. Looking at the duration of the fever, we find a better correlation. The cases fall into fairly distinct groups, with the majority of those where the duration of the fever was short grouped around the lower titer levels and those with a greater number of days with fever around the higher titers. The same features are apparent on a comparison with the highest leukocyte count during the course of the disease.

Discussion.

The investigation has shown that the cases of primary atypical pneumonia that have occurred in Sweden show in all essentials the same features as those described by Anglo-American investigators.

Contrary to the observations made by American investigators, however, even cold agglutination as low as 1/16 had diagnostic value in my series, as has been mentioned before.

The preliminary experiments carried out with a view to demonstrating a specific virus have hitherto been negative.

Of the other clinical laboratory findings the white cell count and the sedimentation râte were attributed diagnostic significance. Contrary to the findings in bacterial pneumonia, the white cell count has been stated to be normal or only moderately raised in this disease. This was found to be the case in the present series also, although the more severe cases often had leukocytosis. The sedimentation râte has been said to be low or only moderately raised. In the present series, high sedimentation rates were common, and this reaction is therefore of no great significance for the differential diagnosis.

The clinical picture showed considerable variation and no uniform and dominating disease type could be distinguished. The gradual onset, with fever, cough, and headache, mentioned by American authors as characteristic, was not the dominating characteristic in my series; an acute, non-specific onset was just as common. The symptoms during the remainder of the course, and the abnormal physical signs, were on the whole the same as those described in American publications, however. A few small differences were observed, however. The initial fever, for instance, was in most cases higher than has been stated as common, and the

typical headache was only present in some of the severest cases, while in the milder cases it was very uncharacteristic.

Treatment with sulfonamide compounds and penicillin does not seem to have had a noticeable effect on the course of the disease.

Summary.

A clinical and etiological study of 112 cases of primary atypical pneumonia occurring during the time of jan. 1945—sept. 1946 in Sweden is reported. Only cases with a positive cold agglutination test are included in the material. The significance of the cold agglutination test compared with some of the laboratory findings and clinical symptoms is discussed.

Bibliography.

1. Adamsson, C. A.: Svensk Läkartidn. *42*, 1389, 1945. — 2. Baker, J. A.: Science *96*, 475, 1942. — 3. Bowen, A.: Amer. J. Roentgenol. *34*, 168, 1935. — 4. Commission on Acute Respiratory Diseases, Am. J. Med. Sci. *209*, 55, 1945. — 5. Commission on Acute Respiratory Diseases, Am. J. Med. Sci. *208*, 742, 1944. — 6. Clough, M. C., Richter, I. M.: Bull. John's Hopkins Hosp. *29*, 86, 1918. — 7. Curnen, E. C., Mirick, G. S., Ziegler, J. E., Thomas, L. F., Horsfall, F. L.: J. clin. invest. *24*, 209, 227, 1945. — 8. Drew, W. R. M., Samuel, E., Ball, M.: Lancet 1,761, 1943. — 9. Dingle, J. H., Abernethy, T. J., Badger, G. F., Buddingh, G. J., Feller, A. E., Langmuir, A. D., Ruesegger, J. M., Wood, W. B. : Am. J. Hyg. *39*, 67, 197, 269, 1944. — 10. Daniels, W. B., Am. J. Med. Sci. *203*, 263, 1942. — 11. Eaton, M. O., Meiklejohn, G., Herick, W.: J. exp. Med. *79*, 649, 1944. — 12. Eaton, M. D., Meiklejohn, G., Herick, W., Corey, M.: J. exp. Med. *80*, 317, 329, 1945. — 13. Finland, M., Peterson, O. L., Allen, H. E., Samper, B. A., Barnes, M. W., Stone, M. B.: J. clin. invest. *24*, 451, 458, 474, 483, 490, 497, 1945. — 14. Horsfall, F. L.: New York State J. Med. *46*, 1810, 1946. — 15. Hedlund, P., Laurell, G., Löfström, G.: Svensk Läkartidn. *42*, 1377, 1945. — 16. Johnsson, B.: Svensk Läkartidn. *43*, 1946. — 17. Kneeland, Y., Smetana, H. F.: Bull. Johns Hopkins Hosp. *67*, 229, 1940. — 18. Longcope W. T.: Ibid. p. 268. — 19. Meiklejohn, G., Eaton, M. D. Herick, W., J. clin. invest. *24*, 241, 1945. — 20. Mirick, G. S., Thomas, L., Curnen, E. C., Horsfall, F. L.: J. exp. Med. *80*, 391, 407, 431, 1944. — 21. Peterson, O. L., Ham, T. H., Finland, M.: Science *97*, 167, 1943. — 22. Reimann, H. A.: J. A. M. A. *111*, 2377, 1938. — 23. Rose, H. M., Molley, E.: Science *98*, 112, 1943. — 24. van Ravenswaay, A. C., Erikson, G. C., Reh. E. P., Siekierski, J. M., Pottash, R. R., Gumbiner, B.: J. A. M. A. *124*, 1, 1944. — 25. Ramsay, H., Scadding, J. G.: Quart. J. Med. *8*, 79, 1939. — 26. Scadding, J. G.: Brit. Med. J. *ii*, 956, 1937.

— 27. Scherstén, B.: Svensk Läkartidn. *43*, 3057, 1946. — 28. Siim, J. C.: Ugeskr. f. Læger, *1*, 1, 1946. — 29. Stenquist, H.: Nord. Med. *30*, 1369, 1946. — 30. Strandell, B., Wågberg-Zander, B.: Svensk Läkartidn *42*, 2266, 1945. — 31. Streeter, G. A., Famer, T. W., Hayes, G. S.: Bull. John's Hopkins Hosp. *75*, 60, 1944. — 32. Turner, J. C.: Nature *151*, 419, 1943. — 33. Turner, R. U. D.: Lancet *i*, 493, 1945. — 34. Weir, J. M., Horsfall, F. L.: J. exp. Med. *72*, 595, 1940. — 35. Young, L. E., Storey, M., Redmond, A. J.: Am. J. Med. Sci. *206*, 756, 1943. — 36. Kullman, C.-E.: To be published.