The Actual and Apparent Number of Pneumocystis Pneumonia Cases in Epidemics

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Abstract. The fundamental premise for an epidemiological investigation of the mass occurrence of any infectious disease is the determination of the common cause. This demand being hard to fulfil in interstitial evtl. atypical pneumonias, the causes of which are considerably different, it was necessary in the first place to evaluate very carefully the literary data published hitherto and dealing with the study of the mass occurrence of atypical pneumonias in children; out of these data we summed up in table-form partly the cases in which the presence of *Pneumocystis carinii* was demonstrated and partly those in which none of the remaining causes of interstitial pneumonia could be proved. We can approach the actual number of pneumocystis pneumonias if, studying the epidemics of this disease, we aim our studies at the relatively "closed" i.e. homologous infant communities, such as institutes for healthy newborns and infants, the so-called "well-baby clinics" with centres for immatures and if we use a sufficiently effective system of multiple controles; among these we must mention in the first place the graphical method of exact local and chronologic correlation of cases diagnosed as interstitial pneumonia of obscure origin to those proved in all respects as pneumocystosis. In this way we examined 1630 infants in two "well-baby clinics" within the period of four years: among them 216 cases were diagnosed as pneumocystosis.

The search for the source of infection in the epidemics of pneumocystosis has up till now been prevalently limited to human sources. But even here one has encountered many difficulties resulting in the fact that all the data on active human sources of such epidemics, published up to date, have remained uncomplete. These difficulties consist before all in the necessity to carry out a retrograde reconstruction of the epidemic back to its onset; in pneumocystosis however such a reconstruction requires an unusually great effort due to the extraordinarily prolonged and rather fluctuating incubation period. Instead of carrying out a reconstruction — one simply took — in most instances — for the initiating case the first deceased infant with pneumocysts found in the lungs. The difficulties in recording all the cases of pneumocystis pneumonia are due — except certain positive results, still sporadic after all — to the failure in finding the parasite in the contents of the respiratory tract in living patients. For this reason some authors published only those cases in which pneumocysts were found post mortem (Table 1). On the other hand some other

Tab. I. Groups of dead cases in epidemics of pneumocystosis

1	2	3	4	5
Austria				
Graz	1941–42	14	Muralter (ex post)	1943
Vienna	1945–51	6	Herbich	1955
Graz	1950–54	8	Schmid	1955
Brazil				
Sao Paulo	1951	3	Brito & Enge	1962
Canada				
Montreal	1958	5	Berdnikoff	1959
Chile				
Santiago	1953	6	Donoso & Meyerstein	1954
Santiago	1955	10	Ariztía & al.	1957
Czechoslovakia				
Plzeň (Pilsen)	1945–51	16	Vaněk (Jirovec)	1951
			Vaněk & Jírovec	1952
Trutnov, Hradec Králové	1949–53	14	Fingerland & Vortel	1957
Olomouc	1951–52	54	Dvořáček	1953
Olomouc	1951–54	(48)	Navrátil & Šmíd	1953
Czechoslovakia	1951–57	(388)	Jírovec	1955
Plzeň	1951–57	48	Linhartová	1958
Central Bohemia	1952–55	21	Benešová & Houštěk	1957
Olomouc	1952–58	(184)	Kodousek	1958
Praha (Prague)	1953–55	(30)	Skřítková & Rokosová	1959
Jihlava	1952–53	8	Pavlica	1955
Slovakia	—	38	Albrecht & Horka	1953
Central Bohemia	1956–57	11	Benešová & Houštěk	1962
Č. Budějovice	1962	7	Hofman	1963
Denmark				
Copenhagen	1947, 1950	5	Gormsen	1950
Copenhagen	1947	(2)	Walther (Friedenreich)	1950
Finland				
Helsingfors	-1950	44	Ahvenainen	1950
Abo	-1950	10	Järvi	1950
France				
Paris	1952	3	Lelong & Le Tan Vinh	1954
Paris	1952	(4)	Le Tan Vinh	1954
Strasbourg	1956–57	12	Fruhling & al.	1958
Germany				
Rostock	1935–38	10	Benecke (ex post)	1938
Rostock	1935–39	(15)	Raspe (Benecke) (ex post)	1939
Berlin	1936–38	8	Ammich (ex post)	1938
Frankfurt/M.	1941–42	12	Asteroth Hana (ex post)	1949
Rostock	1946–47	10	Stopka	1952
Greifswald	1948	5	Stopka	1052
Bremen	1951–52	30	Giese	1952
Marburg, Greifswald	1952	4	Herzberg & al.	1952

Tab. 1. CONTINUED

1	2	3	4	5
Hamburg	1951–56	32	Pliess	1957
Darmstadt	1952–53	27	Pliess	1953
Düsseldorf	1952–53	32	Dickman & al.	1957
Bonn	1952–56	3	Hamperl	1957
Hamburg-Altona	1959	4	Seifert	1960
Tübingen	1958	10	Müller G.	1960
Potsdam	—	25	Meidl	1960
Hungary				
Budapest	1951–52	5	Baĺó & Schuler	1953, 1954
Budapest	1952–53	22	Sipos	1954
Budapest	—	28	Miklós	1960a, b
Iran				
Shiraz	1961–62	6	Post & al.	1961
Italy				
Genova	1952–54	21	Bori Domenica	1955a, b, 1958
Roma	1956–57	4	Maggioni & al.	1958
Ituri (Congo)				
Kilo	1941–44	15	Thijs & Janssens	1963
Kilo	—	3	Thijs & Janssens	1963
Poland				
Danzig (Gdaňsk)	1929–40	46	Giesenbauer (ex post)	1941
Warsaw	1950–55	16	Brzosko & Zulewski	1956
Warsaw	1954–56	(26)	Brzosko & Zalewski	1958
Stetin	1954–56	6	Dominiczak	1959
Roumania				
Yassi	1954	2	Boldescu & al.	1956
Soviet Union				
Moscow	1955–57	6	Žukova	1959
Dusanbe	1962	5	Šelepin	1962
Switzerland				
Basle	1925, 1927	3	Ammich (ex post)	1938
Basle	1941	4	Roulet (ex post)	1941
Zurich	—	35	Deamer & Zollinger	1953

Paragraph 1: Country and place of hospitalisation (evtl. of origin).
Paragraph 2: Date of the epidemic.
Paragraph 3: Number of dead cases reported, Pneumocystis carinii demonstrated. The paranthesis indicates that some preceding cases were compiled.
Paragraph 4: Author evtl. an other expert as parasitologist in the paranthesis.
Paragraph 5: Date of the publication.
The sign —: Not stated by the author.

251 authors included in their reports also the patients suffering from interstitial pneumonia of unknown origin, doubtlessly of multiform character (Table 2). The publications dealing with the evaluation of the complement fixation reaction were in no relation to a certain epidemic unit but in most cases they were based on the survey of samples of sera sent for examination without any regard to the epidemiological viewpoint (Table 3). As far as they did concern a certain unit, they were not detailed enough for epidemiological purposes (KOEVA, ČEREPANOVA 1964).

The cases given in Tab. 1 were collected mostly by pathologists and studied without any consideration of the epidemiological situation. They are however interesting from the epidemiological viewpoint, because they could be used as an index of the frequency of pneumocystosis in a certain group of people; nevertheless it is the question not of a real but only of a minimal number of cases occurred, as there is no such infectious disease of which all the affected people would have died.

A simple sum total of the cases quoted in Tab. 1 could not give even an approximate idea of the minimal number of pneumocystic affections, because some cases were repeatedly reported by the same or by different authors. E.g. out of 54 cases dissected by DVOŘÁČEK (1953) 48 were used in the statistics elaborated by the clinicians NAVRÁTIL and ŠMÍD (1954). It is impossible to ascertain definitely ex post, how many of them were applied in the statistics presented by JÍROVEC (1955) or that published later on by KOŤOUSEK (1958). Furthermore 10 cases published by BENECKE (1938) who was a pathologist, were re-quoted among 15 cases described by the clinician RASPE (1939). From the cases reported by the clinician KOSSEL (1962) many were published also by the pathologist G. MÜLLER (1960). It seems that also in the papers of BRZOSKO and ZALEWSKI (1956, 1958) cases from the years 1954 and 1955 were published twice etc.

A correct conception of any epidemic is bound in the first place to the chronology of cases. Some authors cited in Table 1 consider it however unnecessary to pursue the chronologic progression of their cases (ARIZTIA et al. 1957, MEIDL 1960, MIKLÓS 1960 a, b, DEAMER and ZOLLINGER 1953, in part also THIJS and JANSSENS 1963). Though some of the papers on pneumocystosis do not deal with epidemiological problems, exact chronological data should not be missing in any of the described cases. The cases of pneumocystosis diagnosed on the basis of histological examination and published in Finland (AHVENAINEN 1950, JÄRVI 1950) are given in Table 1 after GORMSEN (1950) who indicates only the end of the period in which they were collected. We are not able to consider whether the Finnish authors had specified in detail all the necessary data, because the respective congress proceedings are inaccessible in our libraries at present.

Similar inaccuracies exist also in the description of cases given in Table 2. The finding of pneumocysts is recorded by authors, quoted in this table, in 55 out of 108 papers. These papers contain only occasional notes on certain chronologic and local epidemiological correlations as regards the relation to histologically proved cases. In some publications, where the series of interstitial pneumonias are described relatively in detail and with a certain exactness, the comments on autopsies are indefinite, the proof of the existence of pneumocysts is missing and so are the microphotographs of histological preparations (FREUDENBERG and TOBLER 1950, TOBLER 1953, BERLIN—HEIMENDAHL and GOETZ 1957, v. HARNACK 1954, ŠMÍD a NAVRÁTIL 1953) or the note on the proof of pneumocysts is of little importance for epidemiological purposes, due to its briefness (ESSICKE 1954, REISETBAUER and MORITSCH 1956). Table 2 reveals a considerable contrast between the small number of cases in which pneumocysts were definitely demonstrated and a great number of those diagnosed only by means of clinical methods, without any regard to the exact chronologic and local correlations. Papers in which the authors omitted to give the number of demonstrated cases of

Tab. 2. Pneumocystosis among cases of "plasma cel" interstitial pneumonia diagnosed by clinical

1	2	3	4	5
Austria				
Graz	1938–52	64	64	64
Schwarzach	1938–56	10	—	—
Vienna	1945–53	27	—	—
Vienna	1950–54	23	17	—
Vienna	1952–53	32	13	13
Vienna	1952–54	52	—	—
Graz	1957	10	6	—
Graz	1955–59	(26)	(10)	—
Bulgary				
Sofia	1954–56	58	48	—
Plovdiv	1959	7	2	2
Chile				
Santiago	—	4	—	—
Santiago	1955–58	34	29	29
Czechoslovakia				
Plzeň (Pilsen)	1945–54	40	33	33
Most	1951–52	7	4	4
Olomouc	1951–52	57	23	23
Opava	1951–52	54	29	— (+)
Olomouc	1951–53	(111)	(36)	—
Olomouc	1951–53	(379)	(95)	(95)
Olomouc	1951–57	(433)	(185)	(185)
Olomouc	1952–53	(66)	(25)	(25)
Bratislava	1952–53	28	16	16
Plzeň	1952–56	34	12	12
Trenčín	—	7	5	5
Opava	1956–57	28	16	16
Bratislava	1961–63	17	6	—
Denmark				
Copenhagen	1951–55	15	5	5
Finland				
Helsingfors	1947–50	51	47	—
Helsingfors	1950–52	72	39	35
Helsingfors	1952–	59	21	—
France				
Mulhouse	1956–57	32	14	10
Mulhouse	1956–62	(50)	—	—
Paris	1959–61	9	3	3
Paris	1959–62	(4)	0	0
Germany				
Düsseldorf	1930–51	146	"2—10 %"	—

6	7	8	9	10
— (+)	Muralter	infants	Muralter	1942
—	—	infants	Martischnig	1958
6	—	infants	Herbich	1955
—		8—23 weeks	Wurnig	1955
13	Braun	7—26 weeks	Reisetbauer & Braun	1955
— (+)	—	infants	Reisetbauer & Moritsch	1956
—		2—2 and half months	Kaloud	1958
—	—	infants	Kaloud	1960
20		1—4 months	Michailov	1957, 1959
			Iden & al.	1959
2		3 and 4 months	Vapcarov & al.	1960
1?	Moreno?	3 infants, one older child	Zelada & al. (cit. Bustamente)	1953
29	—	2—8 months	Bustamente & al.	1956, 1960
33	Vaněk	1—5 and half months	Vaněk & al.	1953
4	Šebek A.	1—5 months	Dvořák & Jírovec	1952, 1953
16	Dvořáček	10 weeks-3½ years	Dvořáček & al.	1953
	Materna	infants	Žák	1953
—	Dvořáček	6 weeks-5½ months	Šmíd & Navrátil	1953
95	Dvořáček	1—10 months	Bárta & al.	1955
(184)	Dvořáček	1—12 months	Nesrsta & al.	1959
(25)	Dvořáček	infants	Navrátil & al.	1954
16	—	1 week-8½ weeks	Michaličková & Kamenský	1954
12	Vaněk	infants	Lukeš & Schwarzkopfová	1957
5	—	infants	Getlík	1956
16	—	4 weeks—19 weeks	Hajduk	1960 a, b.
— (+)	—	infants	Toldyová	1965
2	—	10—12 weeks	Braestrup	1956
—	—	2—5½ months	Ahvenainen & al.	1950
—	—	1—4 months	Ahvenainen & al.	1953
—	—	infants	Halmann & al.	1954
10	Frühling	6—12 weeks	Beyer & al.	1959
17	—	infants	Beyer & al.	1963
3 (+5 alive)	—	10 weeks—6½ months	Le Tan Vinh & al.	1963
4 (alive)	0	2—3 months	Vialatte & al.	1963
—	—	6—17 weeks	Büscher Liselotte & al.	1953
			Gleiss	1956

Tab. 2. CONTINUED

1	2	3	4	5
Halle	1938–40	31	8 (?)	— (+)
Greifswald	1938–44	65	65	
Berlin	1940–42	22	—	3
Berlin	1940–43	15	12	—
Heidelberg	1941–43	12	—	—
Munich	1941–56	379 (graph: 254)	72 (graph)	(+)
Frankfurt/M.	1941–48	53	35 ("66 %")	—
Kiel	—	3	1	—
Berlin-Lichtenberg	1942–43	23		—
Münster	1944–54	25	12	
Munich	1946–47	12	12	12
Rostock	1947–49	39	—	—
Frankfurt/M.	1948–54	3	3	3
Köln	1948–54	121	42	38
Göttingen	1949–53	27	9	—
Leipzig	1949–55	1077	270	—
Jena	1950–51	35	8	—
Jena	1950–51	19	3 (?)	—
Greifswald	1950–53	33	19	—
Jena	1950–57	76	21	— (+)
Hamburg-Eppendorf	1950–53	191	76	—
Dresden-Johannstadt	1950–53	72	—	
Freiburg	1951–53	57	"50 %"	—
Kiel	1951–52	27	2	
Jena	1951–53	8	7	6
Bethel	1951–55	168 (?) ev. 158	79 (?) ev. 73	—
Marburg, Greifswald	1952	9	9	9
Berlin	1952	8	0	0
Düsseldorf, Nürnberg	1952	3	1	1
Oldenburg	1953–57	20	9	—
Köln	1953–54	34	15	—
Essen	1953–54	33	—	11
Leipzig	1952–55	502	125	—
Leipzig	—	72	13	—
Leipzig	1954	7	— (1?)	—
Halle	1954	2	2	2
Würzburg	1954–57	87	16	—
Bad Cannstadt (US Army Hosp.) and Waindlingen	1953–54	4	0	0
Mainz	1955–56	10	4	4
Heidelberg	1956–57	18	7	5
Tübingen	1958–60	11	9	6
Hungary				
Szeged	1949–52	105	45	45

6	7	8	9	10
—	Vaetjen	1—3½ months	Nitschke	1940
—	—	infants	Mannkopf & Ladstätter	1952
—	—	infants	Löhr	1942
—	—	infants	Leiber	1953
—	—	till the age of 11 months	Voss	1943
—	—	1 week—21 weeks	Berlin-Heimendahl & Goetz	1957
— (+)	—	8—10 weeks	Weisse Karla	1951
—	—	infants	Garsche	1951, 1953
—	—	2—13 weeks	Hennig	1943
—	—	2—6 months	Kossenov	1954
—	—	5 days—7 months	Gloggengiesser	1951
— (+)	—	6 weeks—3 months	Brieger	1949
(10 Stopka)			Stopka	1952
3	Manz	infants	Weisse Karla	1955
—	Leupold	infants	Bachmann	1954
—	—	infants	Karte	1954
—	—	infants	Peiper	1957
—	—	infants	Leiber	1953
—	—	infants	Leiber	1952
—	—	infants	Ladstätter & Brieger	1953
— (+)	Holle	6—14 weeks	Essigke	1954
—	—	9—16 weeks	Harnack	1954
—	—	infants	Jacob	1954
—	—	infants	Vivell	1954
—	—	6—8 weeks	Röpke	1953
2	Bruns	12 days—3½ months	Essigke & Vogel	1954
—	—	infants	Müller & Victor	1957
4	Hamperl, Bienengräber	till the age of 14 months	Herzberg	1952
0	0	4—12 weeks	Schlange Hildburg	1953
—	—	6—9 weeks	Klinke & al.	1954
6	—	7 weeks—6 months	Kayser	1958
—	—	infants	Bachmann	1954
—	Sauerbrei	18 days—13 weeks	Fasske & al.	1954
— (+)	Bredt	5 weeks—	Schmöger	1957
—	—	infants	Schmöger	1955
—	—	23 days—50 days	Dietel & Dietel	1955
—	Schönberger	11—13 weeks	Verron	1955
—	—	infants	Neumayer	1955
—	0	10—14 weeks	Sternberg & Rosenthal	1955
4	—	infants	Stopka & al.	1957
—	Randenrath	5 weeks—5 months	Astor Karin & Schreiber	1960
— (+)	Müller G.	8 months + 3 weeks—12½ year	Kossel	1962
—	Korpássy	4—28 weeks	Korpássy & al.	1954

Tab. 2. CONTINUED

1	2	3	4	5
Szeged	1949–52	(95)	(48)	—
Budapest	1951–52	20	12	12
Szeged		19	3	3
Italy				
Milano	1947–52	18	5	1
Milano	1947–53	(21)	—	—
Milano	1947–53	(39)	10	7
Milano	1947–54	(124)	40	
Milano	1947–55	(183)	(57)	(39) (?)
Torino	1952	19	10	—
Torino	—	14	6	4
Milano	1953–54	25	5	5
Bologna	1954	5	3	3
Bologna	1954–55	(20)	—	—
Bologna	1955–57	(13)	(4)	(4)
Bari	1955–58	16	10	6
Bologna	1961	19	12	9
Bologna	1962	5	3	2
Padua	—			—
Catania				
Netherlands				
Heerlen	1955–	81	23	23
Roumania				
Cluj	1956	6	—	—
Soviet Union				
Leningrad	1958–59	32	32	32
Sweden				
Göteborg	1951–54	5	3	3
Switzerland				
German Switzerland	1941–49	707	"28 %"	—
Aarau	1945–51	57	—	—
Bern. Basel	1946–50	380	71	71
Bern	1946–52	104	13	12 (?)
Bern	1946–54	(120)	—	—
Zürich	1958–59	15	2	—
U.S.A				
Santa Monica (Calif.)	—	9	4	4
Pullman (Wash.)	1964	3	2	2

Paragraph 1: Country and place of hospitalisation (evtl. of origin).

Paragraph 2: Date of the epidemic.

Paragraph 3: Number of cases of interstitial pneumonia reported. The paranthesis indicates that some preceding cases were compiled.

Paragraph 4: Number of cases died of interstitial pneumonia reported.

Paragraph 5: Number of cases autopsied.

Paragraph 6: Number of cases in which Pneumocystis carinii was demonstrated.

6	7	8	9	10
.	—	2—3 months	Waltner & al.	1953
2	Sipos & Pál	5—21 weeks	Adler & al.	1952
—	—	infants	Ivády & Páldy	1958
—	—	2—3 months	Toricelli & Bernardi	1952
—	—	infants	Toricelli	1953
(+)	—	1—24 weeks	Toricelli & al.	1953
13	—	1—6 months	Toricelli	1955
— (+)	—	1—6 months	Toricelli	1956
1	Mottura	2—4 months	Colombo & Tauber	1953
4	—	infants	Biressi & al.	1955a, b
5	Malaudra	2—17 weeks	Toricelli & Malaudra	1955
3	Vianello	infants	Malossi & Vianello	1955
4	Businco	infants	Malossi & al.	1955
1	—	1—8 months	Martoni & Domizio	1958
8	De Benedictis	6—13 weeks	Martinelli	1959
10 (1 alive)	—	13 days—90 days	Martoni & al.	1961
2	—	10 weeks—14 months	Martoni & Scorza	1962
2	—	2—3 months	Bentivoglio & Caburro	1958
.	.	.	Palazzo	1957
23	Lankester	infants	Koop Johanna	1964
1	Mihalca	infants	Mihalca & al.	1959
7	Nežinceva	14 days—1 year	Nežinceva	1959
3	—	6—16 weeks	Carlgren & Nathorst-Windahl	1955
1 (?)	—	infants	Tobler	1953
.	—	infants	Baumann	1953
—	—	5—19 weeks	Freudenberg & Tobler	1950
—	Hallauer (?)	infants	Tobler	1953
—	—	8—16 weeks	Tobler	1956
—	—	7 weeks—9 months	Abegg	1960
4	—	10—14 weeks	Falkenbach & al.	1961
2	Chinchinian	7—22 years	Watanabe & al.	1965

Paragraph 7: Name of the pathologist.
Paragraph 8: Age of cases reported.
Paragraph 9: Author.
Paragraph 10: Date of publication.
The sign —: Not stated by the author.
The sign . : Data not available to us.

pneumocystosis, but where they mentioned at least some cases in which pneumocysts were found to determine the presence of the parasite retrospectively from the microphotographs, are marked in the table by a cross in paranthesis.

The designation of different types of interstitial pneumonia recapitulated in Table 2 is not uniform. In this study we are going to consider at least two of them. "Interstitial plasmacell pneumonia", a denomination most frequently used in clinical papers and "Pneumocystis pneumonia" a name introduced by pathologists and parasitologists, both represent histological terms. They should therefore be reserved only for cases in which the presence of great numbers of plasmacells in the interstitial lung tissue or of pneumocysts in the alveolar spaces was demonstrated. In case the presence of pneumocysts was not proved, although the clinical course and the X-ray examination presented a relatively explicit picture speaking for atypical pneumonia, but where the affection could not be brought into a correlation (chronologic and local) with a case of a real pneumocystosis, we are not competent to use another designation than that of "interstitial, evtl. atypical pneumonia". This is necessary to realize all the more that a number of pneumopathies evtl. pathological processes affecting the respiratory tract, especially in infants, is similar to real pneumocystosis and furthermore, because a disease, setting on as pneumocystosis, can frequently be complicated by another etiologically different affection of the respiratory tract. This follows from our own experience as well as from the observations of other authors (Essigke 1954 etc.).

In the diagnosis of pneumocystosis, the occurrence of this disease in the age of 2—4 months or in premature infants may serve only as an aid, because the number of cases occurring beyond this age limit is constantly growing. According to our experience this age limit applies in rough outline merely for epidemics occurring in closed homologous infant communities such as the "well-baby clinics". It is therefore necessary to consider the papers summed up in Table 2, partly from the view of the mentioned age limit and partly from the view of the homogenity of human groups.

As far as the age is concerned, we can see from Tab. 2 that it is given only in total figures if it is given at all and that it fluctuates between the limit of 5 days up to 12 years and a half. From most of the papers it is not clear whether the illness — when it was diagnosed — was just starting, at the peak stage or on the decline. Most frequently, the age of the child had to be derived from the type of the institution to which it was admitted and in which the publication originated. This is of course a factor influencing unfavourably any comparison of the data apart from the fact that every child could have been admitted at a different stage of illness with regard to its onset. The date of the onset of the illness is of outstanding importance especially in infants aged less than one month; this results from the data quoted by twelve authors given in Tab. 2. Pneumonias occurring at this age are namely of a considerably differing etiology. Pneumocystosis at this age is a very rare phenomenon, being — with greatest possibility — caused by intrauterine infection

Tab. 3. KFR examinations of pneumocystosis

1	2	3	4	5	6	7	8	9
Austria								
Vienna	1954–55	15	2(3?)	9(8?)	4	—	Reisetbauer & Moritsch	1956
Bulgary								
Sofia	1961–63	54	—	—	14	—	Koeva & Cerepanova	1964
Czechoslovakia								
Olomouc	1951–53	57	29	29	26	Dvořáček	Dvořáček & al.	1953
Olomouc	1951–53	(379)	(31)	(113)	(235)	Dvořáček	Bárta & al.	1955
Olomouc	1952–53	(66)	(25)	(55)	(11)	Dvořáček	Navrátil & al.	1954
Olomouc	1953–57	(78)	(69)	0	(9)	Dvořáček	Nesrsta & al.	1959
Germany								
Hamburg (?)	1954–55	11	—	10	1	—	Moser Lis	1955
Hamburg (?)	1954–55	(47)	4	(37)	(5)	—	Moser Lis	1959
Oldenburg	1955–56	5	1	4	0	—	Kayser (Moser)	1958
Düsseldorf	1956–57	13	6	7	0	—	Haneke & Roser	1958
Leipzig	—	23	2	20	1	—	Jahn & Roller-Gusinde	1957
Munich	—	148	—	137	11	—	Goetz	1960
Potsdam	—	55	22(25?)	26	7	—	Meidl	1960
Stuttgart	—	13	—	13	0	—	Paschlau (Vivell)	1960
Germany & Switzerland	—	52	—	10	—	—	Vivell & Lips	1958
Netherlands								
Heerlen	1957–59	14	9	6	8	Lankester	Koop Johanna (Dekking)	1964
U.S.A.								
Minneapolis, Little Rock	—	3	2(?)	0(?)	?	—	Goetz	1964

Paragraph 1: Country and place of hospitalisation (evtl. of origin or of laboratory).
Paragraph 2: Date of the epidemic.
Paragraph 3: Number of sera from patients with interstitial pneumonia.
Paragraph 4: Number of positive sera from patients with interstitial pneumonia, Pneumocystis carinii demonstrated.
Paragraph 5: Number of positive sera from patients with interstitial pneumonia, Pneumocystis carinii not demonstrated.
Paragraph 6: Number of negative sera from patients with interstitial pneumonia.
Paragraph 7: Name of the pathologist.
Paragraph 8: Author.
Paragraph 9: Date of publication.
The sign —: Not stated by the author.

(PAVLICA 1962). For the same reason we must consider it a very important factor if the illness sets in after the child had reached the age of four months; this fact is quoted by 30 authors given in Tab. 2. Though pneumocystosis may without any doubt occur also in children aged more than four months, such occurrence is not of a mass character. So far the authors, given in Tab. 2, are reporting a greater number of cases, they indicate neither their chronologic nor local correlation and the onset of the disease in such cases was preceded by a long-term administration of corticosteroids (KOSSEL 1962, G. MÜLLER 1960), by surgical transplantations (RIFKIND 1964, HILL et al. 1964), by the existence of a malignant tumorous process (WATANABE et al. 1965) or by hypogammaglobulinaemia (HUTCHISON 1955 a, b).

On considering the homogenity of human groups reported on in publications ranged in Tab. 2 we see that in their majority these groups are nonhomogenous due to the fact that they are constituted by children coming from the departments where children are treated for various kinds of diseases and from hospitals of different types where there is a strong fluctuation of patients of different age.

All these reasons resulted in the conclusion that in the cases reported by authors given in Tab. 2 it was not the question of merely pneumocystis pneumonia, all the more that many authors cited in the table themselves did not consider the etiology of the affections similar in their clinical symptoms, which they summed up under the common designation "interstitial plasmacell pneumonia". Not even those affections, occurring in children aged 2—4 months, which on the basis of clinical symptoms and an X-ray examination were diagnosed as interstitial pneumonia, can be classified as pneumocystis pneumonia without an exact determination of their local and chronologic correlation to a histologically proved pneumocystis pneumonia, as they also use to be of various etiology.

Though Tab. 2 does not comprise all the papers dealing with interstitial pneumonia of different etiology in infants, because we have omitted: chronic interstitial pneumonias and among the acute ones those diagnosed with certainty as Adam's pneumonia, fungous, yeast, influenza, rickettsial, giant-cell pneumonia, furthermore pneumonias complicating some infectious diseases of infants, those with hyaline membranes etc., it reflects the disproportionate interest in pneumocystosis in different countries, evtl. the gradual growth of this interest. It demonstrates also the periodical occurrence of pneumocystosis in the loci where it had been submitted to a long-term study.

MATERIALS AND METHODS

Homogenous groups of infants for epidemiological studies were supplied by special institutes for healthy newborns and infants, the "well-baby clinics". In our country infants are accepted only for social reasons in such institutions; sick babies cannot be admitted. These institutes are concentrating e.g. newborns whose mothers had died during labour or infants from those households where it is impossible to isolate the newborn from others, eventually sick members of the family; furthermore the newborns the mothers of which are sole breadwinners for one or several children or where the mother after the childbirth falls sick being thus unable to take care of the child or when the intelligence

261 of the mother is unsufficient to such a degree that she can't master the modern principles of the child welfare etc. To these institutes usually the centres for prematures are affiliated. They are managed also by independent head physicians who are not controlling the departments for sick children. For briefness' sake we shall use the term "well-baby clinic" to indicate the institutes for healthy newborns as well as the centres for immatures affiliated to them (the term "well-baby clinic" being used to designate a certain type of institution for infants in the USA, though the purpose of such institutions in America is different from that in our country).

We have been following several such groups for a number of years, up from their birth to the age of one year. We have recorded all cases of pneumonia and from them we eliminated all pneumonias of pneumocystic origin by means of a complex of criteria which included: the clinical picture, in the deceased infants the pathological and anatomical finding, the histological picture and the protozoological examination, in those that survived the intradermal test with pneumocystin, eventually the fixation of the complement in sera and in all cases the epidemiological chronologic and local correlation to a demonstrated pneumocystosis, expressed in graph-form. Detailed data will be published in a series of articles opened by the present paper.

RESULTS

In two well-baby clinics we examined during 4 years and using the above-mentioned method, 1631 infants; from them 50 died of pneumocystis pneumonia caused by the histologically proved parasite and further 166 nurslings were affected with the same disease. We thus diagnosed 216 cases of pneumocystosis on the whole. The ratio of the demonstrated cases of pneumocystosis in deceased infants to other pneumocystic affections amounted approximately to 1 : 4. More detailed numerical data will be included in a further paper. From the mentioned ratio 1 : 4 it results that those who would take for pneumocystosis merely the 50 deceased cases, would base their conception on the existence of only one fourth of the number of cases which could have been proved; they could neither explain sufficiently enough the epidemiological correlation of these cases nor give the reasons for the 100 % letality. Among the 1631 nurslings followed in our study, there occurred, next to the diagnossed 216 pneumocystic affections, further 148 pneumonias of various etiology up to he age of 6 months; none of these 148 pneumonias showed a classical lobar form. Should we include—as it was done by other authors named in Tab. 2—also these cases among those of pneumocystic origin—we would suppose that 364 infants were affected with the same disease.

In order to approximate the actual number of pneumocystic affections occurred it is necessary to follow each infant of a certain community since its birth up to the age of one year; this is a very difficult problem because, since their birth, these children are rather frequently transferred to other places. Usually there exists no exact picture of such shifts in the infants' sojourns though it is of considerable importance for epidemiological studies. I therefore consider it advisable to mention here at least one case:

Š. P. was born on February 29th, 1952 in Jalubí near Uherské Hradiště; according to the custom still frequently observed in Moravian Slovakia, the child was given birth not in the house where the parents were living but in the place from which

the mother came, i.e. in the little house of the grandmother. As the newborn was premature, it was not transferred to the home of the parents, but after being shown to the relatives, it was displaced by an automobile to the delivery department at Uherské Hradiště on March lst; from this it was transferred on the same day to the centre for immature infants affiliated to the well-baby clinic at Kyjov. After gaining the necessary weight of 2820 g it was transferred back to Jalubí on the lst of April. Due to the fact that up to April 5th it lost 120g, it was taken back to the well-baby clinic at Kyjov where it fell sick on April 15th and had therefore to be transferred to the paediatric department for sick nurslings in the hospital at Kyjov. On April 29th it was brought back to the well-baby clinic as cured. On May 12th, while the child was still at the clinic, sings of pneumonia re-occurred and the infant died on May 18th.

To obtain an exact information on this case it was necessary 1) to call at the place of birth and to see there a) the flat of the parents, b) the place where the grandmother was living, c) to inquire at the midwife on the course of the delivery and the following 24 hours, d) to ascertain by inquiries what occurred in the period from April lst up to April 5th, e) to carry out the tests with pneumocystin, f) to catch small rodents in both homesteads. 2) To visit the maternity home at Uherské Hradiště in order to inspect the outpatient records and to obtain some information on the short stay of the infant and the epidemiological situation in this institution at that time. 3) To visit the well-baby clinic at Kyjov and to obtain some information by going through the hospital files (medical record No. 119/52), furthermore to consult the head physician as well as the subordinate physicians, the nurses and the driver of the ambulance car who transported the child. 4) To visit the paediatric department at Kyjov in order to study the medical record No 161/52 and to get acquainted—by personal consultation of the head of the department—with the general epidemiological situation of this department during the stay of our patient. 5) To visit the Institute of Pathological Anatomy in Brno an assistent lecturer of which carried out the post mortem examination and to inspect there the dissection record and the histological preparations.

This information served as a basis for the elaboration of a graph similar to those published in another paper (Kučera, Valoušek 1966).

All 1631 infants were followed in the same details.

To get a correct idea on the chronology of pneumocystic affections occurred in the mentioned two well-baby clinics, we used the graphical method of an exact local and chronologic correlation which will be explained and illustrated in a further paper of this series.

The age in which pneumocystosis occurred in our patients was uniformly determined by the first symptoms speaking for this disease. Even though this phase cannot be determined with an absolute exactness, as shall be specified in one of our next papers, it is possible, by means of this criterion, to obtain a relatively exact statistical picture of the age limit. The age of our patients affected with pneumocystosis can be specified as follows: 61 cases were aged 60—69 days, 44 cases 70—79 days,

263 34 cases 50—59 days, 25 cases 80—89 days. Only in one case the disease broke out within the age limit of 30 days (The infant fell sick on the 16th day of its life and with regard to a positive intradermal test in the mother we may presume an intrauterine origin). At the age from 30 up to 39 days only 7 infants fell sick and only 8 infants were affected at the age of more than 100 days.

In a disease like pneumocystosis, where an exact diagnosis in vivo is difficult, it is necessary to verify every case, suspicious of this infection, by a number of cross controls. The value of such controls lies in the fact that in a given case they may all converge or on the other hand they may display a completely divergent character. In epidemiological work the specification of an exact etiological diagnosis is an utmost necessity. In searching for epidemiological laws we must base our conclusions before all on the cases with most exact diagnosis. In pneumocystosis these are such cases in which the presence of Pneumocystis carinii was clearly demonstrated. The proof can be furnished through a section from the lungs of a deceased patient or it can be contained in a sample obtained by aspiration biopsy in vivo; lately it has been demonstrated in the mucus obtained by tracheal aspiration (Le Tan Vinh et al. 1963) or in laryngeal swabs (Kučera 1965, Kučera and Valoušek 1966). In those cases where such a proof is impossible or in the past had not been furnished, it is absolutely necessary to control the clinical evtl. the X-ray diagnosis (which are indices of only approximative character) by epidemiological relations to other cases in which the parasite had been demonstrated. Only on the basis of these relations, which can be expressed graphically, we can determine the diagnosis of pneumocystis pneumonia; moreover this conclusion must be confirmed in part by a serological demonstration of antibodies during the convalescence, in part by an intradermal test with pneumocystin. All these indirect diagnostic methods are applicable only under the condition that in each case survived there exists a local and chronologic epidemiological correlation to an unquestionably proved case of this affection.

Our experience has shown that pneumocystosis is frequently complicated by the occurrence of other agents, especially by bacterial contamination of lungs or of the upper airways. In pneumocystosis, the same as in other diseases, one individual can simultaneously be attacked by a double- or multiple infection. Literary data indicate e.g. simultaneous occurrence of cryptococcosis (Dick et al. 1957, Winslow and Hathaway 1959, Symmers 1960) or of the cytomegalic inclusion disease (Vaněk 1952, 1953, Mc Millan 1947, Hamperl 1956, Wyatt et al. 1953, Williams et al. 1955, Verran 1955, Kodousek 1958, Ter—Grigorova and Ivanovskaya 1958, Symmers 1960, Miklós 1960 a, b, Kramer et al. 1962). The casual co-existence of viral and bacterial infections is a well-known fact. Why in pneumocystis pneumonia too, there couldn't or shouldn't exist such a co-existence without presupposition, that it isn't but the second infection which conditions the origin of pneumocystosis? If we are acquainted with the epidemiological situation in "closed" communities of children and especially of nurslings, we can't—not even for a moment—doubt of the existence of a simultaneous occurrence of infec-

tions, including pneumocystosis. After all, they had for a long time been the very cause hampering the realization of the social mission of the well-baby clinics. Even in the modern institutes for infants, simultaneous infections in different combinations are occurring rather often, among which the most frequent ones are: varicella, viral infections, rhinitis, adenovirosis, influenza, morbilli, dysenteria, staphylococcal pyodermias, candidiases etc. Most of them may be complicated by pneumonias caused by the very agent responsible for the respective disease (virus of varicella, adenoviruses, the virus of morbilli, staphylococci, monilias etc.). Why shouldn't pneumocystosis run a similar course? In such a situation even the most experienced clinician may fail in specifying the etiologically exact diagnosis. Should he state, by means of clinical methods, the diagnosis of interstitial pneumonia, in which he need not necessarily succeed due to the slightly expressive physical finding, especially if an X-ray examination is missing and if he is dependent on a laboratory examining only laryngeal swabs usually sent for investigation by the subordinate staff, there is no wonder that he takes it for sufficient to make the etiological diagnosis from the mere presence of pneumococci, staphylococci, monilia etc., though it may be the question of a simultaneously occurring second cause or a pneumocytis pneumonia overcovered by a further affection caused by another microbe.

If the process in the lungs runs a longer course and the original pneumocystic affection is overcovered by another type of pneumonia or by some other affection of the upper respiratory tract, the same applies to the pathologist unless he makes most careful and detailed histological studies of the lungs, thus being able to reveal the last remnants of pneumocystic colonies dispersed in isolated groups here and there. As a matter of fact this is why even a negative histological finding need not, though it is a rare phenomenon, speak against the epidemiological assumption, if it is based on an exact chronologic and local correlation (e.g. in twins).

On the other hand our conceptions of pneumocystosis may be considerably simplified by the presumption that all interstitial pneumonias occurring in nurslings are exclusively of pneumocystic origin. Such a conception however results in mixing up of pneumocystosis with other kinds of pneumonia, in a deformed interpretation of the incubation period, in excessively simplified conclusions as regards an effective therapy and in a faulty notion of the frequency, mortality etc.

From the papers mentioned in this article we can draw a further important conclusion which I wish to point out. The occurrence of human pneumocystosis in the form of real epidemics has up to now not been reported among grown-up persons or in communities of infants beyond the age limit of 5 months. The simultaneous occurrence of a greater number of cases among grown-up persons can be observed only after a long-term treatment with corticosteroids (G. Müller 1960, Kossel 1963). On the contrary only sporadic cases of pneumocystosis have been reported in this age group.

Nevertheless it is sporadic pneumocystosis which plays an important role in the epidemiological aspect; this is evident from the fact that all six epidemics which

265 we have had the opportunity to observe, were initiated by sporadic cases of this infection among newborns. This subject will be discussed in one of further papers of this series.

CONCLUSIONS

Papers dealing only with those cases of pneumocystosis which were diagnosed by means of histological methods, enable to conceive only the minimal number of cases occurred. Publications in which pneumocystis pneumonia is not distinguished from other kinds of pneumonia (interstitial evtl. atypical) produce distorted conceptions of a number of epidemiological signs in pneumocystosis. To obtain a more exact conception of the epidemics of this disease, it is necessary to realize a multiple verification of each case by a system of controls, the most important among them being the exact determination of the local and chronologic relation of each case diagnosed by clinical methods to a case diagnosed histologically.

NOTES ON THE REVISION OF OLDER LITERATURE

To work up the table it was necessary to revise in detail all the literature published up to-date on the epidemic occurrence of pneumocystosis and interstitial pneumonia in infants. The revision was aimed at the basic data which would permit to conceive the development in the study of the epidemiology of pneumocystosis. Because a revision of literature has not yet been realized from this viewpoint and citations of the older publications, especially those written in English, are rather fragmentary, it seems reasonable to quote all the publications which we have revised. As requested by the editors, citations are given in abbreviated wording only, full quotations in the column "References" being given merely for the recent publications or those which we wish to point out for epidemiological or other reasons.

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