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Neurological diseases associated with viral and *Mycoplasma pneumoniae* infections

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In 1963 the World Health Organization established a system for the collection and dissemination of information on viral infections and by 1976, laboratories in 49 countries were participating in this scheme. The present study is in two parts: part 1 is an analysis of almost 60 000 reports on neurological disease associated with viral and Mycoplasma pneumoniae *infections reported during the 10-year period 1967–76. This analysis showed a steady increase in the yearly number of reports of viral neurological diseases, which closely followed the general increase in the overall reporting of virus diseases. Likewise, the seasonal pattern was similar to that seen in general for any given virus.*

Over 75% of the cases were in children. Over half of all viral neurological diseases were associated with enteroviruses, while the myxoviruses accounted for almost 30%. Among the myxoviruses, mumps virus was by far the most frequently reported. The polioviruses were the agents most commonly detected in cases of paralytic disease. The other enteroviruses, mumps virus, and the herpesviruses were the most frequently reported viruses in cases of aseptic meningitis or encephalitis. On the other hand, one-third to over one-half of the reports on the myxoviruses (excluding mumps and measles) related to ill-defined clinical conditions.

Part 2 of the study deals in particular with viruses whose role in neurological disease is less well documented. One laboratory reported an outbreak of adenoviral aseptic meningitis in Czechoslovakia, while another described neurological disease associated with M. pneumoniae *infection in Finland. Part 2 also includes a detailed appraisal of viral infections diagnosed in the Netherlands during the period 1973–76. The results are very similar to those routinely reported.*

In 1963, the World Health Organization established a system for the collection and dissemination of information on viral infections other than those due to arboviruses. By the end of 1976, virus laboratories in 49 countries were participating in the scheme. The first two studies dealt with circumscribed groups of viruses, namely, enteroviruses other than polioviruses (*1*) and respiratory viruses (*2*). The third study (*3*) concentrated on virus infections having a fatal outcome rather than on particular groups of viruses. By limiting the study of a specific outcome, it was hoped to reduce to a minimum the influence of differences in performance and interest between laboratories when comparing groups of countries. The results of the study were encouraging enough to justify initiating the present study, which is limited to another possible outcome, namely, neurological diseases associated with viral and *Mycoplasma pneumoniae* infections. In this paper, the term "viral infections" will be used to include those due to *M. pneumoniae*.

The study consists of two parts. Part 1 is an analysis of neurological diseases associated with viral infections reported to the WHO Virus Reporting System during the period 1967–76. Part 2 (pages 304-310) is a more detailed investigation of viral association with neurological disease by three laboratories in Czechoslovakia, Finland, and the Netherlands.

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PART 1. WORLDWIDE VIRAL NEUROLOGICAL INFECTIONS

Countries participating in the WHO Virus Reporting System were eligible for inclusion in the study provided that, during the period 1967–76, they had reported a minimum of 25 recorded instances of neurological infections associated with any one specific virus. Viruses were included in the study only if an association with a neurological condition had been noted by at least one country in at least 25 reports in any one year during the same period.

Once a country had been accepted into the study, all reports on neurological conditions associated with any of the viruses eligible for the study were included.

The study is limited to the 10-year period 1967–76, i.e., the period during which the information is available on magnetic tape and can be computer-processed and tabulated. The neurological clinical manifestations are presented under three headings: paralysis, meningitis/encephalitis, and other conditions, a limitation dictated by the coding scheme built into the WHO Virus Reporting System.

The viruses are discussed here separately, and the different types of adenovirus, coxsackievirus A and B, echovirus, etc., are mentioned when of interest. No mention is made of the antigenic variation of influenza virus A, but it is assumed that up to 1968, variants of A/Singapore/1/57(H2N2) were reported, and that after the summer of 1968, A/Hong Kong/1/68(H3N2) or its variants were reported. No distinction is made between the antigenic variants of influenza virus B.

RESULTS

Information from laboratories in 30 countries is included in the present study. These countries were divided into 6 groups according to geographical location and level of industrial development. By far the largest group, consisting of 15 countries, is in Europe, while the other groups consist of 2–4 countries each:

Africa (excluding North Africa): Kenya, Madagascar, Senegal, South Africa.

Middle and South America: Argentina, Mexico, Trinidad and Tobago.

Asia (excluding the Pacific): Malaysia, Thailand.

Eastern Mediterranean and North Africa: Egypt, Morocco.

Europe: Austria, Belgium, Czechoslovakia, Denmark, Finland, France, German Democratic Republic, Federal Republic of Germany, Hungary, Ireland, Netherlands, Norway, Sweden, Switzerland, United Kingdom.

North America and the Pacific: Australia, Canada, Japan, United States of America.

The study comprises 59 281 reports of viral neurological infections. Although only 19 out of the 30 countries (63%) are in the European or North American and Pacific regions, laboratories from these two groups provided about 90% of the reports. In other words only about 10% of the reports came from developing countries.

The viruses that fulfilled the conditions for inclusion in the study are shown in Table 1.

Virus frequencies

From Table 1, it can be seen that enteroviruses were noted in over 55% and myxoviruses in almost 30% of the total number of reports analysed. The herpesviruses and the adenoviruses followed in frequency: 8% and 6% respectively. Lymphocytic choriomeningitis virus (LCM) was recorded in less than 0.5% of the reports and *M. pneumoniae* in a little over 1%.

In Europe and in the North American and Pacific regions, the relative frequencies with which the different virus groups were found to be associated with neurological conditions were similar to the overall picture. In contrast, in the developing countries, i.e., in the African, Middle and South American, Asian, Eastern Mediterranean, and North African regions, the enteroviruses, mostly polioviruses, were associated with 97–100% of the total number of viral neurological conditions reported.

Within the group of myxoviruses, mumps virus predominated by far, accounting for 78% of the total number of reports on myxoviruses in Europe and 68% in North America and the Pacific. Influenza virus A was next in order of frequency (between 8% and 11%), while the other myxoviruses accounted for between 2% and 8%.

Within the herpesvirus group, herpes simplex virus accounted for 73% in Europe and 82% in North America and the Pacific. The other two viruses, i.e., varicella-zoster and cytomegalovirus, were noted in 6–14% of the reports on herpesviruses.

Typing of viruses

Where facilities for typing were available, the viruses were reported by type.

Coxsackievirus A. Type 9 largely predominated in Europe and in North America and the Pacific, constituting 80–81% of all those typed. A small number were not typed: 5% in Europe and 7% in North America and the Pacific. No figures are available for Africa, the only other region where coxsackievirus A was reported.

Table 1. Reports of viral neurological infections by country group, 1967–76

Associated viruses	Africa		Middle & South America		Asia excl. Pacific		E. Mediterranean & N. Africa		Europe		N. America & Pacific		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Enteroviruses														
coxsackievirus A	315	16.0	0	0.0	11	0.7	0	0.0	1 646	3.9	378	3.5	2 350	4.0
coxsackievirus B	148	7.5	3	0.1	8	0.5	0	0.0	4 921	11.5	1 395	13.0	6 475	10.9
echovirus	59	3.0	40	1.9	15	1.0	0	0.0	13 147	30.8	4 934	46.1	18 195	30.7
poliovirus	1380	70.2	2051	96.8	1506	97.8	294	100.0	782	1.8	166	1.5	6 179	10.4
Herpesviruses														
herpes simplex virus	22	1.1	9	0.4	0	0.0	0	0.0	2 591	6.1	734	6.9	3 356	5.7
varicella-zoster virus	0	0.0	0	0.0	0	0.0	0	0.0	514	1.2	104	1.0	618	1.0
cytomegalovirus	2	0.1	0	0.0	0	0.0	0	0.0	465	1.1	52	0.5	519	0.9
Adenoviruses	10	0.5	6	0.3	0	0.0	0	0.0	2 784	6.5	583	5.4	3 383	5.7
Myxoviruses														
influenza virus A	6	0.3	4	0.2	0	0.0	0	0.0	1 144	2.7	262	2.4	1 416	2.4
influenza virus B	2	0.1	4	0.2	0	0.0	0	0.0	319	0.7	87	0.8	412	0.7
parainfluenza virus	1	0.1	2	0.1	0	0.0	0	0.0	525	1.2	134	1.3	662	1.1
respiratory syncytial virus	0	0.0	0	0.0	0	0.0	0	0.0	356	0.8	65	0.6	421	0.7
mumps virus	7	0.4	0	0.0	0	0.0	0	0.0	11 623	27.3	1 566	14.6	13 196	22.3
measles virus	15	0.8	0	0.0	0	0.0	0	0.0	898	2.1	190	1.8	1 103	1.9
Arenaviruses														
LCM virus	0	0.0	0	0.0	0	0.0	0	0.0	198	0.5	12	0.1	210	0.4
M. pneumoniae	0	0.0	0	0.0	0	0.0	0	0.0	738	1.7	48	0.4	786	1.3
Totals	1967	100.0	2119	100.0	1540	100.0	294	100.0	42 651	100.0	10 710	100.0	59 281	100.0

Coxsackievirus B. Almost all were typed in Europe and in North America and the Pacific. The percentages of those typed represented by types 2, 3, 4, and 5 are shown below:

Coxsackievirus B type	*Europe*	*N. America & Pacific*
2	22	20
3	22	18
4	18	17
5	31	41
Totals	93	96

Echovirus. Almost all echoviruses were typed and all types were encountered. Types 4, 6, 9, 11, 19 and 30 were found most often but their relative frequencies (% of all echoviruses typed) in Europe differed markedly from those in North America and the Pacific:

Echovirus type	*Europe*	*N. America & Pacific*
4	7	6
6	18	12
9	13	32
11	7	12
19	15	3
30	19	14
Totals	79	79

Poliovirus. Poliovirus was reported in all regions. Type 1 predominated by far in Africa (75% of the total), Middle and South America (96%), and Asia (82%) and, to a lesser extent, in the Eastern Mediterranean and North Africa (58%). In Europe, type 1 was still the predominant type but it accounted for only about 40% of all the polioviruses reported in the present study, followed by type 2 (31%) and type 3 (28%). In North America and the Pacific, the relative frequencies of the 3 types in descending order were: type 3 (39%), type 2 (38%), and type 1 (23%).

Herpes simplex virus. Only about 6–7% were typed in Europe and in North America and the Pacific. Type 1 predominated (87% in Europe; 82% in North America and the Pacific).

Adenoviruses. Almost three-quarters of the adenoviruses reported by laboratories in North America and the Pacific, and over two-thirds of those reported by European laboratories were typed. The types implicated in neurological diseases included types 1–17, 21, 26, 28–31. However, types 1, 2, 3, 5 and 7 predominated, the percentages being as shown below:

Adenovirus type	*Europe*	*N. America & Pacific*
1	21	23
2	28	28
3	10	17
5	14	10
7	20	16
Total	93	94

Parainfluenza viruses. Only types 1 and 3 figure in the study. Type 3 accounted for 63% of the total neurological conditions associated with parainfluenza virus in Europe and 74% in North America and the Pacific.

Time trends

The overall trend showed a gradual increase in the number of reports of viral neurological infections over the 10 years under study but the annual increment has been greatest during the last few years (Table 2). The increase in the number of reports of neurological infections more or less followed the pattern for the total number of reports of virus infections received by WHO, i.e., irrespective of the clinical condition (unpublished data).

The fluctuations in the annual number of reports on neurological disease associated with coxsackievirus A and B, echovirus, and poliovirus followed more or less the pattern for the total number of reports on these viruses. However, neurological conditions associated with coxsackievirus B infections showed—contrary to the total number of reports—a sustained increase during 1975 and 1976.

The fluctuations in coxsackievirus A reports reflected changes in the number of reports on type 9. Among coxsackievirus B, types 1 and 6 were reported relatively infrequently in association with neuro-

Table 2. Reports of viral neurological infections by year of collection or receipt of specimen, 1967–76

Associated viruses	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	Total
Enteroviruses											
coxsackievirus A	209	167	278	262	160	212	246	196	235	385	2 350
coxsackievirus B	648	599	369	641	705	537	673	720	752	831	6 475
echovirus	2042	2085	1421	1580	1686	1023	1507	2144	3026	1681	18 195
poliovirus	710	907	494	807	794	817	365	496	511	278	6 179
Herpesviruses											
herpes simplex virus	157	183	192	228	302	327	391	506	524	546	3 356
varicella-zoster virus	20	26	26	36	53	44	88	105	98	122	618
cytomegalovirus	22	40	19	38	43	52	68	60	62	115	519
Adenoviruses	223	243	267	270	290	271	485	344	486	504	3 383
Myxoviruses											
influenza virus A	9	82	188	77	62	101	136	87	289	385	1 416
influenza virus B	5	29	31	20	46	12	21	70	25	153	412
parainfluenza virus	39	40	45	50	62	39	85	83	95	124	662
respiratory syncytial virus	14	23	19	24	22	27	53	47	99	93	421
mumps virus	1017	548	874	1618	1410	1350	1394	1233	2197	1555	13 196
measles virus	38	40	46	101	112	101	139	121	192	213	1 103
Arenaviruses											
LCM virus	28	11	13	24	22	5	30	45	28	4	210
M. pneumoniae	22	14	7	15	51	44	116	122	173	222	786
Totals	5203	5037	4289	5791	5820	4962	5797	6379	8792	7211	59 281

logical diseases; in most years, type 5 predominated, particularly in 1970–74 and in 1976. Many cases of neurological disease were associated with coxsackievirus type 2 in 1967 and 1971, with type 3 in 1967, 1968, 1970, and 1974, and with type 4 in 1975 and 1976.

The high numbers of reports of echovirus-associated neurological conditions referred mainly to types 6, 9, and 30 in 1967, types 6 and 30 in 1968, types 4 and 11 in 1971, and types 19 and 30 in 1974 and 1975. Echovirus type 9 was also reported in comparatively large numbers in 1969, 1970, and 1973, but this had little impact on the total number of reports of echovirus-associated neurological disease.

The fluctuations in the reported incidence of poliovirus-associated neurological disease were reflected in the incidence of poliomyelitis cases (mostly type 1) in a small number of countries (Table 3).

Table 3. Number of reported cases of poliomyelitis in various countries, 1967–76

Country	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976
Kenya	–	–	–	–	–	14	74	135	44	70
Malaysia	–	–	–	–	255	476	–	1	2	0
Mexico	354	460	168	613	163	48	–	–	97	–
Morocco	–	–	–	–	–	–	25	19	101	–
South Africa	144	208	34	45	86	114	36	130	70	3
Thailand	77	68	159	36	100	38	75	78	41	100

The marked rise in the number of reports of neurological conditions in which an adenovirus was noted was not matched by a similar increase in the total number of reports received by WHO on these viruses, which, on the contrary, declined during 1975 and 1976. The increase in the number of neurological reports associated mainly with type 1, type 2 and, to a lesser extent, type 5. The number of reports on neurological conditions associated with adenovirus type 7 rose rapidly to a peak in 1973 but quickly declined thereafter. The total number of adenovirus type 7 infections reported showed a similar sharp increase in 1973 followed by a marked decline.

A very marked increase in the number of reports of neurological disease associated with influenza virus A was noted in 1975 and 1976. However, this was not matched by the increase in the total number of reports on influenza virus A. A/Port Chalmers/73 was the dominant virus in the winter of 1975 and A/Victoria/3/75 was dominant in the winter of 1976 (*4*). It should be noted that the first sharp increase in reports on influenza virus A, including those associated with a neurological condition, commenced in 1969 and was related to the advent of A/Hong Kong/68.

Reports on neurological disease associated with influenza virus B showed three successive peaks, in 1971, 1974, and 1976. However, the relative increase in the number of infections associated with neurological disease was not matched by a similar increase in the total number of reports on influenza virus B.

The reports on neurological disease associated with parainfluenza virus and respiratory syncytial virus followed fairly closely the pattern depicted by the total number of reports on these viruses.

With the exception of LCM virus, the reported incidence of other viruses followed the general pattern of a progressive yearly increase. Cases of LCM-associated neurological disease were reported in very small numbers by a few countries. Of the total of 210 reports, 148 (70.5%) came from Hungary.

Seasonal patterns

Except for the adenoviruses, there is a close correlation between the seasonal variation of viral-associated neurological infections and the seasonal variation in reports of virus infections in general. Thus, in the Northern Hemisphere (Table 4) neurological manifestations were reported in association with influenza virus A and respiratory syncytial virus most frequently from December to March inclusive and with influenza virus B from January to April inclusive. Parainfluenza viruses associated with neurological disease were most frequently reported during the months October, November, and December, but were reported also in large numbers during the summers of 1973 and 1975.

Reports of herpes simplex virus, varicella-zoster virus, cytomegalovirus, LCM, and *M. pneumoniae* associated with neurological disease, were more frequent during the winter, but did not show a pronounced seasonal pattern. In contrast, reports of mumps and measles viruses increased late in the winter and in the spring.

Reports on adenovirus infections in which a neurological condition was mentioned were fairly common during winter but were most frequent during the summer.

Reports on neurological conditions associated with enteroviruses showed a pronounced seasonal variation, particularly those associated with coxsackieviruses A and B and echovirus, which were most frequent in summer and early autumn. Although reports of poliovirus-associated neurological disease increased during the same part of the year, there was an even more pronounced peak in January. This somewhat unexpected winter peak was related to the severe outbreak of poliomyelitis in Malaysia in the winter of 1972.

Table 4. Reports of viral neurological infections by month of collection or receipt of specimen—Northern Hemisphere, 1967–76

Associated virus	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Enteroviruses													
coxsackievirus A	63	19	33	48	91	222	369	390	251	204	102	51	1 843
coxsackievirus B	96	59	61	116	234	515	1155	1392	885	613	291	112	5 529
echovirus	632	186	230	283	683	1362	2667	3514	2852	1964	857	379	15 609
poliovirus	604	447	357	355	272	377	439	503	491	358	386	360	4 949
Herpesviruses													
herpes simplex virus	341	241	237	246	260	241	259	255	236	285	232	175	3 008
varicella-zoster	79	29	43	55	49	59	70	44	31	49	43	41	592
cytomegalovirus	45	39	48	36	35	45	40	30	39	58	50	27	492
Adenoviruses	264	226	239	264	255	285	320	335	255	263	223	174	3 103
Myxoviruses													
influenza virus A	326	375	243	81	22	11	11	5	12	10	31	202	1 329
influenza virus B	60	105	73	52	27	14	10	5	3	6	9	29	393
parainfluenza virus	37	34	39	46	38	67	50	32	35	72	74	51	575
respiratory syncytial virus	101	66	54	25	11	9	8	8	6	16	34	49	387
mumps virus	1140	909	1231	1276	1184	1194	1096	815	569	767	944	939	12 064
measles virus	88	84	96	114	105	114	93	69	67	78	74	66	1 048
Arenaviruses													
LCM virus	22	19	25	19	22	14	7	11	6	15	27	19	206
M. pneumoniae	88	53	67	47	72	66	59	69	55	66	59	59	760
Totals	3986	2891	3076	3063	3360	4595	6653	7477	5793	4824	3436	2733	51 887

A mirror-image of the above relationships holds for viruses reported in sufficiently large numbers in the Southern Hemisphere.

Age distribution

Except for herpes simplex virus, varicella-zoster, and LCM, viral neurological disease was reported mostly in children, but the relative frequency differed among the viruses (Table 5). Almost 90% of reports on adenovirus, over 90% of reports on parainfluenza virus and RSV, and over 95% of reports on poliovirus concerned children, particularly those below 5 years of age.

Between 80% and 85% of the cases of mumps and measles with neurological manifestations concerned children, mainly in the age group 5–14 years.

A little over half of the herpes simplex virus, 66.6% of the varicella-zoster and 85.3% of the LCM neurological infections were in adults, particularly in the age group 25–59 years, which accounted for about 30% of the total number of reports on both herpes simplex virus and varicella-zoster and over 50% of those on LCM.

Clinical neurological manifestations

Three broad clinical groups were distinguished: paralysis, meningitis/encephalitis, and "others" (Table 6). No indication is available of the extent and site of the paralysis or even whether it was transient or persistent. The category "others" covers a very wide range of neurological conditions, including convulsions, and may not necessarily indicate a viral infection of the CNS. Considering that paralysis and meningitis/encephalitis may both be taken to indicate a direct infection of the nervous system, the associated viruses included in the study fall into 4 distinct groups according to frequency of association with neurological disease.

Group 1, in which over 90% of the virus infections reported were associated with a frank neurological condition: these included infections due to echoviruses, polioviruses, mumps, and LCM viruses. Very few of the reports on mumps virus, only 1% of those on echovirus, and 2% of those on LCM virus mentioned paralysis among the clinical manifestations. In contrast, in 87% of the reports on polioviruses,

Table 5. Reports of viral neurological infections according to age,[a] 1967–76

Associated virus	0–14 years		⩾ 15 years		Total No.
	No.	%	No.	%	
Enteroviruses					
coxsackievirus A	1 620	74.4	557	25.6	2 177
coxsackievirus B	4 268	72.5	1 620	27.5	5 888
echovirus	12 016	70.9	4 933	29.1	16 949
poliovirus	5 629	97.1	171	2.9	5 800
Herpesviruses					
herpes simplex virus	1 500	49.2	1 546	50.8	3 046
varicella-zoster virus	195	33.4	389	66.6	584
cytomegalovirus	352	70.7	146	29.3	498
Adenoviruses	2 824	89.0	350	11.0	3 174
Myxoviruses					
influenza virus A	880	65.2	469	34.8	1 349
influenza virus B	262	67.2	128	32.8	390
parainfluenza virus	571	92.5	46	7.5	617
respiratory syncytial virus	374	93.0	28	7.0	402
mumps virus	10 099	80.7	2 417	19.3	12 516
measles virus	876	84.0	167	16.0	1 043
Arenaviruses					
LCM virus	28	14.7	162	85.3	190
M. pneumoniae	443	59.0	308	41.0	751
Totals	41 937	75.7	13 437	24.3	55 374

[a] In 3907 reports the age was unknown.

paralysis was noted as the principal clinical feature. However, a marked difference was seen between developing and developed countries. In the developing regions, between 88% and 100% of the reported polioviruses were associated with paralysis, as against 32–40% in the developed world.

Group 2, in which 80–90% of virus infections were associated with definite neurological disease. This group included coxsackieviruses A and B, herpes simplex virus, varicella-zoster virus, measles virus, and *M. pneumoniae*. Again the ratio between paralysis and meningitis/encephalitis differed among the viruses. At one extreme, 22% of the total reported cases of varicella zoster showed paralysis. At the other extreme, only 2–4% of the reports on coxsackievirus B, herpes simplex virus, and measles virus mentioned paralysis. In between, 7–8% of coxsackievirus A and *M. pneumoniae* infections showed paralysis.

Group 3, in which 50–80% of the virus infections were associated with well-defined neurological manifestations; adenovirus, influenza viruses A and B, and cytomegalovirus belonged to this group. While only 4% of the adenoviral and influenza virus infections were reported to be associated with paralysis, such an association was reported in 17% of cytomegalovirus infections.

Group 4, in which less than 50% of the virus infections gave rise to definite neurological manifestations. This group comprised parainfluenza and repiratory syncytial viruses; less than 4% of the total number of reports on either virus mentioned paralysis.

Table 6. Reports of viral neurological infections according to the main manifestation, 1967–76

Associated virus	Europe, North America, and Pacific				Other country groups				All country groups			
	Paralysis	Meningitis &/or encephalitis	Other manifestations	Total	Paralysis	Meningitis &/or encephalitis	Other manifestations	Total	Paralysis	Meningitis &/or encephalitis	Other manifestations	Total
Enteroviruses												
coxsackievirus A	48	1 700	276	2 024	134	118	74	326	182	1 818	350	2 350
coxsackievirus B	124	5 258	934	6 316	34	114	11	159	158	5 372	945	6 475
echovirus	157	16 501	1 423	18 081	26	83	5	114	183	16 584	1 428	18 195
poliovirus	359	377	212	948	4 999	92	140	5 231	5 358	469	352	6 179
Herpesviruses												
herpes simplex virus	142	2 573	610	3 325	1	24	6	31	143	2 597	616	3 356
varicella-zoster virus	136	379	103	618	0	0	0	0	136	379	103	618
cytomegalovirus	90	211	216	517	0	1	1	2	90	212	217	519
Adenoviruses	138	2 008	1 221	3 367	4	7	5	16	142	2 015	1 226	3 383
Myxoviruses												
influenza virus A	50	728	628	1 406	3	6	1	10	53	734	629	1 416
influenza virus B	16	232	158	406	2	1	3	6	18	233	161	412
parainfluenza virus	12	300	347	659	1	2	0	3	13	302	347	662
respiratory syncytial virus	16	179	226	421	0	0	0	0	16	179	226	421
mumps virus	54	12 480	655	13 189	0	7	0	7	54	12 487	655	13 196
measles virus	32	826	230	1 088	4	7	4	15	36	833	234	1 103
Arenaviruses												
LCM virus	4	204	2	210	0	0	0	0	4	204	2	210
M. pneumoniae	57	619	110	786	0	0	0	0	57	619	110	786
Totals	1 435	44 575	7 351	53 361	5 208	462	250	5 920	6 643	45 037	7 601	59 281

PART 2. VIRAL NEUROLOGICAL INFECTIONS INVESTIGATED IN MORE DETAIL BY THREE SELECTED LABORATORIES

The part played by enteroviruses and mumps virus in neurological disease is already well established. In 1972, a review of the information available in the WHO Virus Reporting System revealed, among other features, an unexpectedly high proportion of neurological conditions were associated with infections with adenovirus, myxoviruses (other than mumps virus), and mycoplasma. Detailed investigations of the role of viruses other than enteroviruses and mumps virus in neurological disease were therefore undertaken at the following three laboratories:

— Department of Virology, National Institute of Public Health, Bilthoven, Netherlands
— Department of Epidemiology and Microbiology, Institute of Hygiene and Epidemiology, Prague, Czechoslovakia
— Virus Serological Department, Central Public Health Laboratory, Helsinki, Finland.

In these laboratories, the viral or mycoplasmal agents were identified only after they had been subjected to thorough laboratory examinations. An attempt was also made to obtain data on the final clinical diagnosis at discharge to supplement the information on clinical signs noted initially. The clinical diagnosis was coded in much more detail than in the more general study reported in Part 1 (pages 298-304).

RESULTS

Bilthoven, Netherlands

During the period 1973–76 inclusive, the regular contributions to the WHO Virus Reporting System comprised 826 reports on viral neurological infections from this laboratory. Virus infections other than enteroviruses and mumps amounted to 199 cases (or

24.1%). Of these, 138 (or 69.3%) are included in the detailed study: the others were excluded because of either an unsatisfactory clinical diagnosis or unsubstantiated laboratory findings. The clinical grounds for exclusion included a revision of the diagnosis as well as rejection of ill-defined clinical manifestations, such as convulsions. Unsubstantiated laboratory diagnosis included the incrimination of possible etiological agents other than viruses or negative serological findings in spite of virus isolation.

The relative frequencies of the individual viruses in the original group of 199 cases and in the revised group of 138 cases are very similar (Table 7). The findings reported below concern only the revised group of 138 cases.

Adenovirus headed the list of viruses and accounted for almost 38% of cases. Herpes simplex virus and varicella-zoster virus followed with relative frequencies of 18% and 17%, respectively. In other words these 3 viruses together accounted for almost three-quarters of the cases. The other viruses were the subject of between 2 and 10 reports each.

Table 7. Relative frequency of viral neurological infections, other than enteroviral and mumps, reported by the Netherlands during the period 1973–76

	Reports included in the WHO Virus Reporting System (Part 1)		Reports included in the detailed studies (Part 2)	
Associated virus	No.	%	No.	%
Herpesviruses				
herpes simplex virus	34	17.1	25	18.1
varicella-zoster virus	29	14.6	24	17.4
cytomegalovirus	14	7.0	2	1.4
Adenoviruses	85	42.7	52	37.9
Myxoviruses				
influenza virus A	11	5.5	6	4.3
influenza virus B	7	3.5	7	5.1
parainfluenza virus	4	2.0	3	2.2
respiratory syncytial virus	3	1.5	2	1.4
measles virus	12	6.0	10	7.2
Arenaviruses				
LCM virus	0	0.0	0	0.0
M. pneumoniae	0	0.0	0	0.0
More than one virus	0	0.0	7	5.1
Totals	199	100.0	138	100.0

Adenovirus. Of the 52 adenovirus-associated cases, 19 were diagnosed solely on serological (complement-fixation) evidence. In these cases, the adenovirus type could not be determined. In 33 cases an adenovirus was isolated and typed. In 26 of these cases, a complement-fixation test was carried out on paired sera and showed a four-fold rise in titre in 17 cases. In 9 cases, an initial high titre either remained the same or showed a two-fold rise. The predominant types were 1, 2, 3, and 7. Forty-eight cases were in children and the highest proportion was in the age group 1–4 years. The neurological manifestations most frequently seen were meningitis (28 cases) and encephalitis (19 cases). Two cases were diagnosed as meningoencephalitis, 2 cases were labelled "atonia", and in 1 case meningism was noted. The adenovirus type was apparently unrelated to the type of neurological manifestation.

Herpes simplex virus. In 20 out of 25 cases, the diagnosis was made solely on serological evidence, i.e., a four-fold or greater rise in the complement-fixing titre in paired sera. In 5 cases herpes simplex virus was isolated and the infection was confirmed serologically in 3 of these cases. Typing of 3 of the 5 isolates indicated that they were type 1. Herpes simplex virus infection was encountered as frequently in the young as in adults: 12 cases in children below 10 years of age and 13 in adults aged 15 years and over. Encephalitis was the most frequent diagnosis (12 cases), followed by meningitis (7 cases), but in 5 cases a diagnosis of meningoencephalitis was made. One case of facial paresis was recorded.

Varicella-zoster. In 23 cases, the diagnosis was made solely on the evidence of a four-fold or greater rise in the complement-fixing titre in paired sera. In one case, the virus was isolated and the diagnosis confirmed serologically. Nine cases were in the age group 1–9 years, 1 case in the age group 10–14 years, and 14 cases in the age group 15 years and over. Two of the cases were diagnosed as meningism, 7 as meningitis, 3 as encephalitis, and 2 as meningoencephalitis. One notable feature was the frequency with which "paralysis" was recorded. In a total of 10 cases (i.e., over 40%), the following diagnoses were made:

Age group (years)	*No. cases*	*Diagnosis*
1–4	1	Ascending paralysis
10–14	1	Facial paralysis
15–24	1	Facial paresis
	1	Hemiparesis
	1	Subacute paresis of right glosso-pharyngeal nerve
25–58	2	Facial paralysis
	1	Facial paresis
⩾60	2	Facial paresis

Thus, in 8 of the 10 cases, a cranial nerve was affected.

Other viruses. In only 3 cases of influenza virus B and 2 cases of parainfluenza virus was the diagnosis based on both isolation and serology. Isolation only was the basis of diagnosis in 1 case of influenza virus A and 3 cases of influenza virus B. All the remaining cases were diagnosed on serological evidence only: influenza virus A (5), influenza virus B (1), parainfluenza virus (1), respiratory syncytial virus (2), cytomegalovirus (1), and measles virus (10).

Influenza virus A was diagnosed equally frequently in the young below 5 years of age and in adults aged 15–29 years: there were 3 cases in each age bracket.

In contrast, influenza virus B, parainfluenza virus, and RSV were encountered only in children. Seven cases of measles were in the age group 1–4 years, one case in an infant below 1 year of age, one case in the age-group 5–9 years of age, and another in the age group 15–24 years. The two cytomegalovirus cases were over 25 years of age.

The clinical picture was mainly that of meningitis or encephalitis. The 13 cases of meningitis were distributed as follows: influenza virus A (2), influenza virus B (4), parainfluenza virus (2), respiratory syncytial virus (2), and measles (3). There were 9 cases of encephalitis: influenza virus A (2), influenza virus B (2), parainfluenza virus (1), and measles virus (4). In addition, meningism was present in 1 case of measles, meningoencephalitis in 2 cases of influenza A and 1 of measles, and paralysis in 1 case of influenza B, 1 case of measles, and 2 cases of cytomegalovirus infection. Of the cases with paralysis, no further information was given on the influenza B case, the measles case was diagnosed as myeloneuritis and the 2 cytomegalovirus cases as myelitis and radiculitis cum myelitis.

In 7 cases more than one virus was diagnosed:

Virus	*No. of cases*	*Paralysis*
Meningism	1	adenovirus 1, parainfluenza virus 1 and coxsackievirus B4
Meningitis	1	herpes simplex virus and mumps virus
Encephalitis	2	adenovirus (not typed) and herpes simplex virus
	1	varicella-zoster, measles and coxsackievirus B4
Meningoencephalitis	1	herpes simplex virus and echovirus 6
	1	herpes simplex virus and varicella-zoster virus

Prague, Czechoslovakia

Between 1972 and 1975, a series of outbreaks of respiratory tract infection associated with neurological manifestations occurred in various parts of Czechoslovakia, most of them in Plzeň and Ostrava. The details of these outbreaks are summarized in Table 8. In all cases, the disease was attributed to adenovirus infection. The accompanying neurological manifestations were aseptic meningitis in the majority of cases and meningism in a smaller number. There were 107 cases altogether, nearly all of them in children. The age group 5–9 years was most heavily affected. In all cases, the disease was benign and there was full recovery.

Isolation of adenovirus, either from stools or from the nasopharynx, was possible in 52 cases, the prevailing types being 3 and 7, although types 1, 2, and 5 were also found in some outbreaks. Serological evidence (CF test) of infection was obtained in a total of 90 cases, and in 38 of these the virus had also been isolated.

Helsinki, Finland

From 1971, outbreaks of acute respiratory disease associated with *Mycoplasma pneumoniae* were reported from different parts of Finland. The outbreaks reached a peak in 1972, continued during 1974 and 1975, and began to abate in 1976. A number of these cases of *M. pneumoniae* acute respiratory disease showed neurological signs. However, during these prolonged outbreaks, cases of neurological disease occurred where there were no signs of acute respiratory infection but in which there was laboratory evidence of *M. pneumoniae* infection (a four-fold or more rise in CF titre in paired sera).

Altogether, during the period 1973–76 inclusive, *M. pneumoniae* was diagnosed by the laboratory in 69 cases in which neurological involvement was a leading clinical manifestation. However, in 12 of these cases, viruses were also implicated, and in 2 cases the leading neurological sign was convulsions. *M. pneumoniae* was the only agent incriminated by the laboratory in 55 cases of definite neurological involvement. These 55 cases are the subject of the present study.

The first case was reported in June 1973 and was diagnosed as aseptic meningitis. By the end of 1973, 12 cases had been noted. In 1974, there were 23 cases and in 1975 there were 16. In 1976, only 4 cases were diagnosed.

In 33 cases the main clinical manifestation was aseptic meningitis, in 14 cases it was encephalitis, in 4 cases meningoencephalitis, in 3 Guillain-Barré syndrome, and in 1 case hemiplegia. Fever was noted in 49 cases, respiratory involvement in 13 cases (signs of upper respiratory infection in 10 and of lower respiratory infection in 3), enteritis in 7 cases, and skin rash in 3 cases. In 1 case of meningitis, endocarditis was also diagnosed.

Table 8. Reports of adenovirus infection associated with neurological disease in Czechoslovakia, 1972–75

Date	Place	No. cases (age group)	Clinical diagnosis	Isolation of adenovirus	Serological evidence	Isolation + serology	Adenovirus types
Nov. 1972 –Jan. 1973	Plzeň	27 (5–9)[a]	URD,[b] conjunctivitis, aseptic meningitis[c]	27 (from faeces, 10 also from naso-pharynx	23	23	2, 3
Late summer & autumn, 1973	Ostrava	31 (5–14)[d]	Aseptic meningitis[e]	15 (from naso-pharynx)	26	10	1, 3, 5, 7
Nov. 1973	Plzeň C. Budejovice	1 (5–9) 2 adults	URD, aseptic meningitis	–	3	–	–
Late summer & autumn, 1974	Ostrava	32 (1–24, half in age group 5–9)[f]	URD, aseptic meningitis (2 cases of meningism + 1 of encephalitis)	8	28	4	1, 3, 7
Aug./Sept., 1974	Plzeň	5 (5–14)	URD, meningism	–	5	–	–
	Usti, Brno	6 (1–14)	URD, meningism (1 meningitis)	2	5	1	7
1975	Plzeň + 2 new areas	3 (6 mths, 1–4, 15–24)	Lower respiratory infection, meningism, meningitis[g]		3		–

[a] One child in age group 10–14.
[b] URD = upper respiratory disease.
[c] Lymphadenitis also in few cases.
[d] Two cases in age group 1–4, one in age group 15–24.
[e] Also enteritis in one case and tonsillitis in another.
[f] One case in age group 25–59.
[g] One case had enteritis and meningitis.

Table 9. Reports of *Mycoplasma pneumoniae*-associated neurological infections according to age and the main clinical manifestation, Finland, 1973–76

Age (years)	Menin-gitis	Enceph-alitis	Meningo-enceph-alitis	Guillain-Barré syndrome	Hemi-plegia	Total
< 1	1	1	1	–	–	3
1 – 4	8	4	1	–	–	13
5 – 9	2	1	–	–	–	3
10 – 14	3	2	1	–	–	6
Subtotal children 0–14 years						
	14	8	3	–	–	25
15 – 24	1	4	–	–	–	5
25 – 59	16	2	1	3	1	23
⩾ 60	2	–	–	–	–	2
Subtotal adults ⩾ 15 years						
	19	6	1	3	1	30
Totals	33	14	4	3	1	55

All age groups were represented: 25 cases were in children and 30 cases in adults (Table 9).

DISCUSSION

Viral infections of the central nervous system are a fairly common occurrence, especially in children. Clinically they comprise a wide spectrum of conditions, usually designated according to the primary anatomical site involved, hence the descriptive terms aseptic meningitis, encephalitis, meningoencephalitis, encephalomyelitis, etc.

For the purposes of the WHO Virus Reporting System, an attempt was made in 1967 to differentiate between:

(*a*) definite neurological involvement without paralysis, e.g., aseptic meningitis, encephalitis,

(*b*) definite neurological involvement with paralysis, including cranial nerve affection, and

(*c*) other conditions that may not indicate a direct involvement of the central nervous system, e.g., meningism, convulsions.

Many viruses can cause neurological disease and it is estimated that a viral (or mycoplasma) agent can be identified in 50–70% of suspected viral neurological infections in laboratories with adequate facilities and trained personnel (*5*).

The laboratory method used for identifying a viral neurological infection depends on the kind of specimen the laboratory can obtain from the attending physician, the laboratory facilities, the available clinical data and epidemiological information and also the suspected viral agent (*6*). Thus, in the case of the enteroviruses a diagnosis is made in almost all cases on the evidence of isolation, since a diagnosis based on serology would require too large a battery of tests in view of the great number of known enteroviruses. For adenovirus infections, however, the complement-fixation test is a most useful single procedure for serological diagnosis, but other methods are needed to determine the antigenic type. In the case of cytomegalovirus infections, the method of choice has "traditionally" been the direct isolation of the virus from urine, although the CF test is now used more frequently. On the other hand, in the case of *M. pneumoniae*, few virus laboratories have the facilities for culturing the organism, but they include the CF antigen among the antigens used for viral serology. Because of the time required and the technical complexity of the procedure, the isolation of measles virus is rarely attempted, i.e., the diagnosis rests on serological findings. The need to use mice or guinea pigs for the isolation of LCM virus prevents routine isolation of this virus.

In itself, the recovery of a virus from a patient does not necessarily mean that the illness can be attributed to that particular agent. However, if the virus is isolated from the brain or the cerebrospinal fluid, there is a very high probability that any neurological manifestations can be attributed to that agent. Similarly, a viral diagnosis is much more credible if the isolation is coupled with serological evidence of infection. It appears that the laboratories participating in the WHO Virus Reporting System very rarely had access either to material from the CNS or the CSF, and in only a small proportion of cases did they carry out both isolation attempts and serological examinations on the same patient. On the other hand, in the Part 2 studies, the diagnosis is frequently based on both isolation and serological tests except for the *M. pneumoniae* outbreak in Finland, where the diagnosis was made solely on serological evidence. A comparison between the findings in Parts 1 and 2 is of special importance in the case of viruses whose possible etiological role in neurological disease is doubtful or has not been well-documented. The most important among these are the adenoviruses, the influenza and parainfluenza viruses, and respiratory syncytial virus.

Notwithstanding the shortcomings of Part 1, the study confirms that viral neurological disease is seen mostly in children (over 75%), that its incidence varies from year to year, and that it is seen throughout the year, although in the Northern Hemisphere the largest numbers are almost always encountered during late summer and early autumn (*5*, *7*). The agents most commonly diagnosed in infections associated with neurological disease were enteroviruses. In Europe, the enteroviruses accounted for 48% of all viral infections accompanied by neurological involvement, in North America and the Pacific for 64%. In the developing world they accounted for 97–100%. There was a striking difference between the developing and the developed world in the number of instances in which polioviruses were diagnosed as causes of neurological disease and in the frequency of paralytic poliomyelitis. Out of a total of 6179 cases of laboratory-confirmed poliovirus infection reported in the Part 1 study, 5231 cases (85%) were reported by the 11 laboratories from the developing world. Furthermore, of the total number of 5358 cases of paralytic poliomyelitis, the developing countries accounted for 4999 cases, or 93%. In the developed world, immunization programmes against poliomyelitis have greatly reduced prevalence of the disease. In the developing world, low vaccination coverage is, as expected, accompanied by frequent outbreaks of the disease (*8*).

In the developed world, most outbreaks of aseptic meningitis/encephalitis were associated with a limited number of enteroviruses, mainly the coxsackieviruses and echoviruses. Of the coxsackieviruses A, type 9 predominated, of the coxsackieviruses B, types 2, 3, 4 and 5 were common, and of the echoviruses, types 4, 6, 9, 11, 19 and 30 were frequently encountered. The outbreaks were irregular in pattern: a given type struck only one or a few countries at a time, recurred without any regular time interval and in general without an epidemiological progression from one country to another. In a few instances, one type caused epidemics extending beyond one season, e.g., in the United Kingdom in 1974 only 5 cases of aseptic meningitis were associated with echovirus 30, while an outbreak starting in 1975 with 197 cases extended into 1976 with a total of 229 cases for that year.

Enterovirus 71 was not included in the WHO Virus Reporting System until 1974, after recognition of the strain in an outbreak of aseptic meningitis/encephalitis in Sweden in 1973 (*9*). Of the 20 isolations reported to WHO from this outbreak, 11 were from cases with neurological symptoms. Retrospectively, two outbreaks of viral neurological disease, one in Melbourne, Australia in 1972–73 (*10*), and one in

Bulgaria in 1975 associated with paralysis and several fatal cases (*11*), have been confirmed to be due to enterovirus 71.

Only a very small proportion of enterovirus infections cause apparent neurological disease but the ease with which enteroviruses spread in children of the developed world is striking. The neurological diseases caused by enteroviruses other than the polioviruses are, in general, self-limited benign conditions. But a poliovirus introduced in a community with a high vaccination coverage presents a real danger to the pockets of non-vaccinated, non-protected groups of the population. This was witnessed in 1970 in Texas, USA, where a cluster of 13 cases occurred in two communities among the non-vaccinated, all of them associated with poliovirus type 1 (*12*). Similarly, in 1972, 11 cases of poliomyelitis occurred in non-vaccinated students belonging to a Christian sect in Connecticut, USA (*13*). In the Netherlands in 1971 an outbreak of 43 cases occurred in a group of the population that rejected vaccination on religious grounds (*14*). More recently, in 1978, an outbreak involving 108 cases was reported in the same religious group (*15*). It is of interest to note that in the USA a live trivalent vaccine is used, while in the Netherlands a killed vaccine is administered together with DTP vaccine.

Mumps virus is recognized as one of the commonest viral causes of neurological disease. In the present study it accounted for 27% of all laboratory-diagnosed cases in Europe and 15% in North America and the Pacific. It is doubtful whether immunization against mumps accounts for this difference. Again, aseptic meningitis was the most frequent clinical manifestation. The enterovirus and mumps virus together were diagnosed in over three-quarters of the cases reported to WHO from these two groups of countries. In a little less than a quarter of the cases a wide spectrum of viral agents was identified. The possibility that a number of these agents, e.g., herpesviruses and measles virus, can infect the central nervous system has been well-documented and the findings in the present study confirm previously reported instances. On the other hand, the role of adenoviruses, influenza and parainfluenza viruses, and respiratory syncytial virus, in the causation of neurological disease has not been definitely established.

In the Netherlands (Part 2 of the present study) the findings over the period 1973–76 tally very closely with the results obtained in the developed world as a whole. In 24% of the total number of reported cases, viruses other than enterovirus or mumps were identified, and in almost 70% of these cases the laboratory findings established fairly conclusively the viral nature of the etiological agent. However, among these 138 cases, 51 cases were attributed to a herpesvirus infection, a finding that agrees with established views, but 52 cases were associated with an adenovirus whose role in neurological infection has been given little credence in the past.

However, in Czechoslovakia, the adenovirus outbreaks in Plzeň in 1972 and in Ostrava in 1973 and 1974 lend support to the possible role of adenovirus in neurological infections. The outbreaks were primarily of upper respiratory infection among schoolchildren, aseptic meningitis was considered as a complication. No other viral agents could be detected. In a sizeable proportion of cases evidence of an adenovirus infection was established by both isolation and serology. The virus was frequently recovered from the nasopharynx, a site that would tend to confirm an infection by the adenovirus (it has been recognized that isolation from faeces does not in many instances relate to a concurrent infection). It may be of interest to note that two of these outbreaks occurred in winter, in contrast to the findings in the Northern Hemisphere in the Part 1 study and in the Netherlands in the Part 2 study, where the peak incidence was in summer, i.e., when the enteroviruses are most commonly found. There were no reports of similar outbreaks from other parts of the world. Nevertheless, a close look at the role of adenoviruses in neurological disease is undoubtedly warranted.

The laboratory findings in the Netherlands implicating myxoviruses in neurological disease are less clear. For example, the number of influenza cases with neurological manifestations bears little relation to the actual toll from influenza. No cases of influenza CNS infections were diagnosed in the winter of 1973 but two were identified in the winter of 1974, two in the winter of 1975, and two in the winter of 1976. The winter of 1973 was marked by large outbreaks of influenza (and of excess mortality from respiratory diseases) caused by A/England/42/72.The 1973/74 season was rather calm, but the 1974/75 season was marked by outbreaks caused by A/Port Chalmers/72 and in the 1975/76 season A/Victoria/75 made its presence felt in the Netherlands (*4*).

On the other hand, diagnosis of the seven cases of influenza B with neurological manifestations in January and February, 1974, tallies with the widespread outbreaks of influenza B during that season. Furthermore it was in 1974 that there were indications in the USA of an association between influenza B and Reye's syndrome (*16*).

The 3 cases of parainfluenza and 2 cases of respiratory syncytial virus infection with signs of meningitis or encephalitis were all in children and all showed signs of respiratory infection. The numbers undoubtedly represent a very small fraction of the cases of croup or bronchiolitis and may well be evidence of genuine CNS complications.

The outbreak of *M. pneumoniae* infection in Finland strongly suggests that this organism plays a role in

the causation of various types of neurological dysfunction in children and young adults. Clinically, this picture of neurological involvement does not usually differ from that caused by viruses except for a high incidence of associated respiratory infection (*6*). In the present study, respiratory infection was present in one-quarter of cases, although it is most probable that the respiratory symptoms were overlooked when the more severe neurological disease was reported. Laboratory investigations in Finland showed that a significant rise in *Mycoplasma* antibodies could be detected concurrently with a rise in antibodies to meningococcus or *Haemophilus influenzae* in cases of bacterial meningitis. Therefore, in cases reported as aseptic meningitis associated with *M. pneumoniae* a non-specific rise in *Mycoplasma* antibodies cannot be entirely ruled out. The experience in Finland would warrant the inclusion of CF antigen against *M. pneumoniae* in the battery of serological tests routinely carried out in virus laboratories.

So far the laboratory methods used for the diagnosis of viral infections have rested on either isolation or serology. Isolation is time-consuming and, as mentioned above, does not necessarily mean *per se* a concurrent infection. Serological confirmation of the infection requires an even longer time in order to allow for the rise in antibody titres to be significant. The time lag between the clinical and laboratory diagnosis has disassociated the laboratory from the actual care of the patient. In other words, the laboratory investigations have become an epidemiological rather than a diagnostic tool. In turn, this has had its effects on the relationship between the clinician and the laboratory. The clinician finds the laboratory investigations irrelevant to his patient's immediate needs. The laboratory cannot very well press for more precise information from the clinician, since little can be offered in return. In this context, an accurate assessment of the role of a given virus detected by the laboratory and the disease condition of the patient is, to say the least, not always an easy undertaking.

Laboratory techniques for rapid diagnosis of viral infections are at present being developed (*17*). Techniques under consideration for the detection of viral antigens are immunofluorescence, the immunoperoxidase reaction, and enzyme immunoassay. Similar techniques are being used for the detection of early, specific IgM antibodies under circumstances that warrant the diagnosis of the virus infection involved. The techniques promise to be both sensitive and specific for a very large number of etiological agents. These techniques would allow the laboratory to give a diagnosis within 3–4 hours of receiving the specimen. In this way, it will be possible for a dialogue to be established between the clinician and the virus laboratory. For the clinician, the laboratory would help in the choice of therapy, provide a sound basis for prognosis, and assist him in control of nosocomial infections.

Conversely, once the laboratory findings are relevant to the diagnosis and care of the patient an accurate assessment of the etiological role of an agent detected by the laboratory becomes part of the diagnosis. With such developments in the future, perhaps a number of the questions raised in this paper will be answered.

RÉSUMÉ

TROUBLES NEUROLOGIQUES ASSOCIÉS À DES INFECTIONS VIRALES ET À *MYCOPLASMA PNEUMONIAE*

La première partie de l'article a trait aux résultats de l'analyse des rapports provenant de laboratoires de 30 pays sur les troubles neurologiques associés à des infections à virus ou à *Mycoplasma pneumoniae*, qui sont parvenus au *Virus Reporting System* de l'OMS de 1967 à 1976. Ces troubles comprennent la paralysie, la méningite et l'encéphalite, auxquelles s'ajoute un groupe de manifestations neurologiques cliniques mal définies. La deuxième partie est consacrée à des études plus approfondies du rôle joué par les divers virus responsables des atteintes neurologiques signalées, qui ont été faites par trois laboratoires en Finlande, aux Pays-Bas et en Tchécoslovaquie.

Plus de 55% des 59 281 rapports auxquels se réfère la première partie mentionnent les entérovirus comme cause de maladie neurologique, et près de 30% les myxovirus, alors que les herpèsvirus et les adénovirus ne sont incriminés que dans 8% et 6% des rapports respectivement. Le virus de la chorio-méningite lymphocytaire (CML) figure dans moins de 0,5% des rapports et *M. pneumoniae* dans un peu plus de 1%. Les rapports provenaient à concurrence d'environ 90% de laboratoires de pays développés. Presque tous ceux qui émanaient de pays du tiers monde se rapportaient aux entérovirus, et principalement aux poliovirus. En fait, 85% de tous les cas de poliomyélite confirmés par un laboratoire et 93% de ceux ayant entraîné une paralysie ont été enregistrés dans les pays en développement. Dans le groupe des myxovirus, le virus des oreillons a été le plus souvent cité (77% des infections à myxovirus), suivi par le virus grippal de type A (8%), la part des autres types de myxovirus variant entre 2 et 6%. Dans le groupe des virus herpétiques, les virus de l'herpès simplex ont été les plus souvent mentionnés (dans 75% des rapports concernant ce groupe).

La courbe ascendante, au cours de la période considérée (1967–1976), des rapports signalant des maladies neurologiques associées à des virus a été à peu près parallèle à celle traduisant l'augmentation du nombre des rapports

concernant des infections virales reçus à l'OMS; et l'une et l'autre ont subi les mêmes fluctuations annuelles et saisonnières.

Les cas enregistrés affectaient des enfants à concurrence de plus de 75%; seuls les herpèsvirus, le virus de la varicelle et du zona et le virus CML ont été plus souvent signalés chez les adultes.

Sur le plan clinique, les entérovirus, le virus des oreillons et le virus CML ont été ceux les plus souvent associés à des atteintes du type méningite/encéphalite, tandis que, parmi les entérovirus, les poliovirus étaient associés le plus souvent à une paralysie.

En ce qui concerne les myxovirus, et si l'on exclut les virus des oreillons et de la rougeole, un tiers à plus de la moitié des rapports concernaient des manifestations cliniques neurologiques mal définies.

Dans la deuxième partie de l'article, consacrée aux enquêtes faites par trois laboratoires, les travaux du laboratoire des Pays-Bas sont commentés d'abord. Ils ont porté sur les troubles neurologiques associés à des virus autres que les entérovirus et le virus des oreillons pendant la période 1973–1976. Sur 138 rapports plus particulièrement étudiés par ce laboratoire, 52 avaient trait aux adénovirus et concernaient surtout des enfants, 25 à des infections à herpèsvirus ayant frappé dans une proportion à peu près égale des enfants et des adultes, et 23 à des virus de la varicelle et du zona dont 10 ont été à l'origine de paralysie. Un nombre limité de cas mettaient en cause d'autres virus: virus grippal de type A et B, virus paragrippal, virus respiratoire syncytial, cytomégalovirus et virus de la rougeole.

Les travaux du laboratoire tchèque ont porté sur les infections à adénovirus qui ont provoqué une maladie neurologique pendant la période 1972–1975, au cours de laquelle ont été enregistrées, principalement chez les écoliers, trois épidémies de maladie respiratoire avec complications neurologiques. Dans une forte proportion des cas, la responsabilité d'un adénovirus a été confirmée par une épreuve sérologique aussi bien que par l'isolement de cet agent, aucun autre virus n'ayant pu être identifié.

Le laboratoire finlandais a fait rapport sur les troubles neurologiques provoqués par une infection à *M. pneumoniae* diagnostiquée durant la période 1973–1976. Des poussées épidémiques dues à cet agent s'étaient manifestées dès 1971 pour atteindre leur intensité maximale en 1972, se maintenir pendant les années 1974–1975 et enfin décroître en 1976. Dans l'étude effectuée (1973–1976), *M. pneumoniae* a été identifié comme seul agent étiologique dans 55 cas où les manifestations cliniques principales étaient de type neurologique. Ces cas ont été enregistrés dans tous les groupes d'âge puisqu'ils concernaient 25 enfants et 30 adultes.

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