AN OUTBREAK OF DISEASE BELIEVED TO HAVE BEEN CAUSED BY ECHO 9 VIRUS *

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In recent years an increasing number of reports has been published of outbreaks of nonfatal neurotropic disease of obscure origin. One group of these diseases is distinguished from the rest by the presence in many cases of a rash, usually described as rubelliform.

The first outbreak of such an illness in England was described by Parry and Good in 1949.[8] Subsequently, epidemics of meningitis-with-rash have been observed in many parts of the world, and while no causative agent has been discovered in some of these epidemics, ECHO viruses have been incriminated in others. In 1956 meningitis attributed to infection by ECHO 9 viruses was seen in several parts of Europe, including the United Kingdom, and the present paper gives an account of an epidemic which occurred in the small Lancashire town of Newton-le-Willows in the summer of that year.

Method, Material and Terrain

The investigation was carried out from general practice, the aim being to define the clinical picture and to elucidate the epidemiology of the disease.

The population of the town numbered 21,000 and, of these, 4,000 were on the practice "list" of the writer. This sample group was distributed fairly evenly among the rest of the population at risk. Patients were seen at home or at the office, and were visited at frequent intervals. Whenever possible, entire families in which a case had occurred were interrogated at intervals in the search for early signs in new cases.

Newton-le-Willows, although situated in one of the most populous parts of England, remains quite self-contained. It is still surrounded by agricultural land, and much the greater part of the population works and goes to school in the town. It is not a suburb or "dormitory." The place consists of three housing estates, an old village, and a 19th century railway village disposed about the periphery of a large open space of fields, and connected by a ring road, intersecting railway lines accentuating the division of the area into "neighborhoods."

School attendance registers were examined and schoolmasters questioned about the effect of the epidemic on their pupils.

From the data collected from patients, their physicians, close contacts, and from schoolmasters and their registers, a distinct pattern of the spread of the disease could be discerned, but it has not been possible to establish

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TABLE 1
Weekly Morbidity Rate, July 1–October 21

Week No...	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Number of new cases	13	31	37	29	17	13	6	4	2	1	3	4	0	5	1	1

that a single agent was responsible for all the illness seen. Only nine patients were investigated for evidence of infection by ECHO 9 virus. Six showed a significant rise in titer of antibodies over a period, and strains were isolated from the feces of four. Other serologic and virologic investigations in these and many other people were all without positive result.

The evidence that the epidemic to be described is attributable to a single agent is therefore circumstantial.

PROGRESS OF THE EPIDEMIC

In June, 1956, children began to fall sick with headache, vomiting, fever, drowsiness, fleeting limb pains and sometimes rash. None of the 10 local doctors, some of them having had many years of experience in general practice in the town, could recall having seen similar cases previously. The

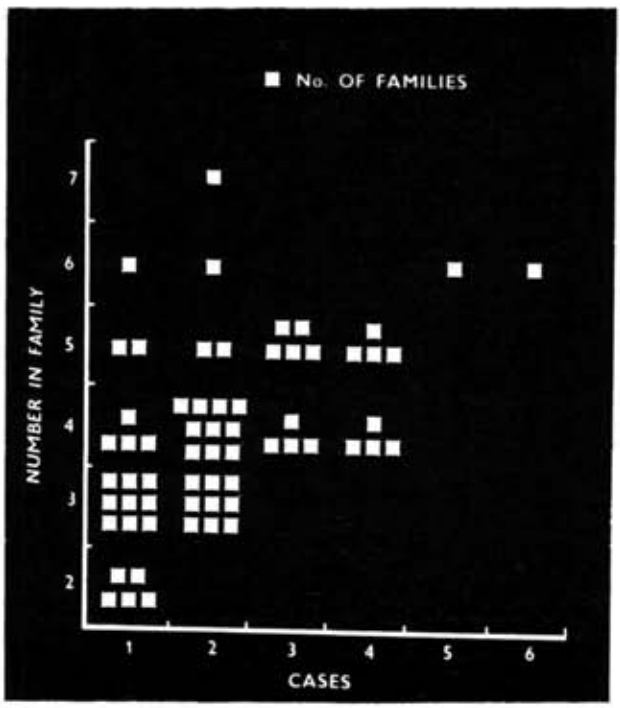


FIG. 1. The case rate in family groups. Each square represents one family. The vertical scale refers to the size of the family, the horizontal to the number of cases in it.

TABLE 2
Incidence of Cases by Age and Sex

Age Group....	0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–
Male	12	23	6	3	3	7	7	7	5	3	2	0	2
Female	8	21	10	2	2	8	6	7	2	5	0	0	1

peak of the epidemic was reached in the third week of July; after the end of August there were few new cases (table 1).

One hundred sixty-two cases were seen in the sample of the population under review between July 1 and October 1, a prevalence of 3.5% of the

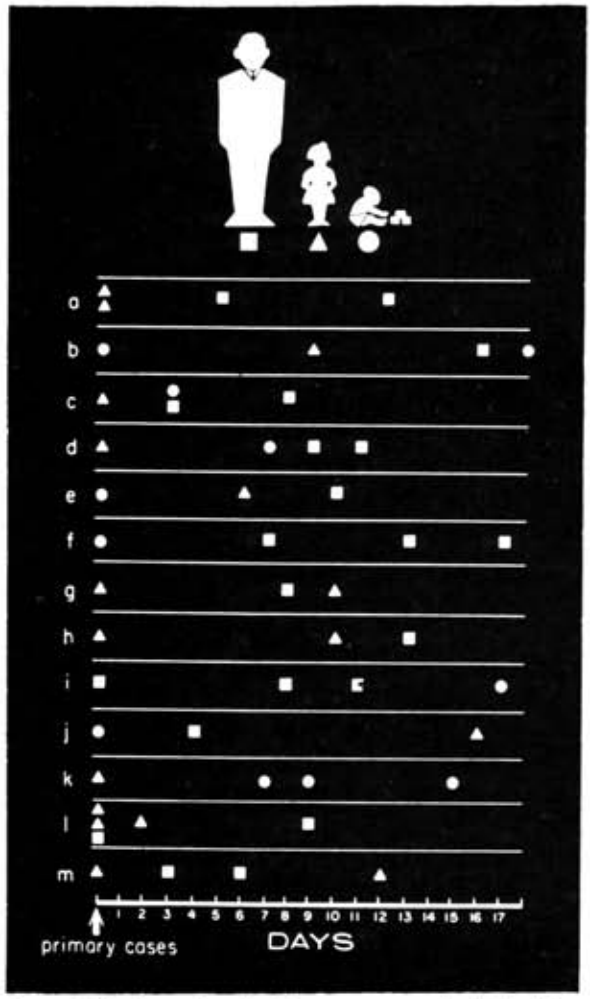


FIG. 2. The interval in days elapsing between cases in 13 family outbreaks (a-m). Two or more individuals sometimes fell sick on the same day. The key indicates adult, school-aged and preschool-aged cases.

practice. It is known that some people, family contacts of cases seen, although themselves ill, continued at work without reporting sick. Others fell ill while on holiday elsewhere. The true prevalence must therefore have been higher than 3.5%.

Isolated cases in families were unusual. As a rule, at least two members of a household were affected (figure 1), commonly at an interval of about five days (figure 2). Sometimes whole families were ill at the same time.

The primary case in family outbreaks was nearly always a young child (figure 3). Children, numerically speaking, bore the brunt of the epidemic,

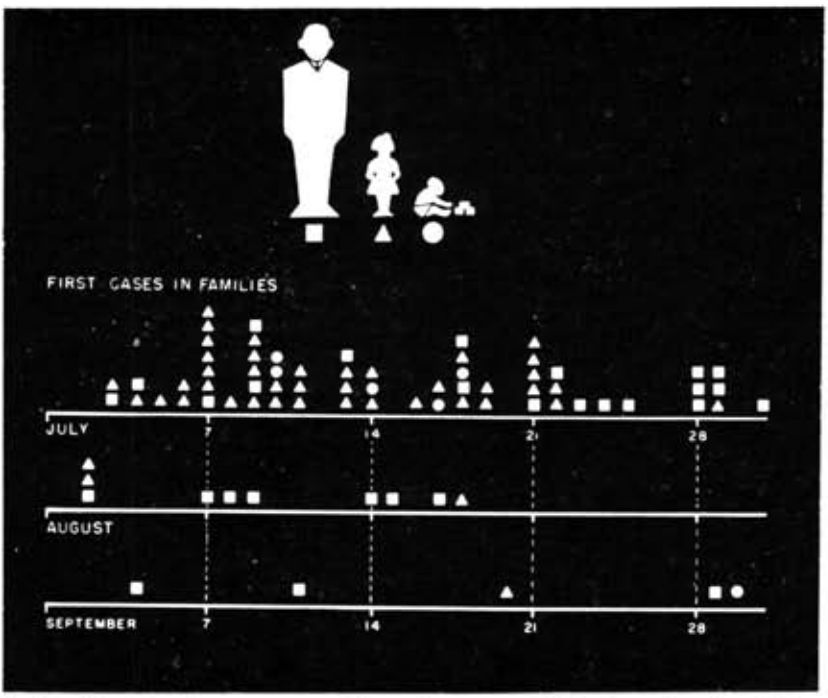


FIG. 3. The time of appearance of the primary case in family outbreaks. Where two people fell ill at the same time, only one is shown. The key distinguishes adult, school-aged and preschool-aged cases, each square on the figure representing one person.

and there was an abrupt fall in the case incidence in the 10-to-14 year age group (table 2), most marked among 12 year olds, although there was no corresponding fall in the number of children of this age at risk in the population (figure 5).

The incidence of new primary cases in family outbreaks was sharply reduced in the fourth week of July (figure 3), after which new cases were mostly secondary cases in households (figure 4). The junior schools, which serve children up to the age of 12, closed for the summer holiday at the end of the third week of July. Reference to the registers of all the schools revealed that attendance in three primary schools was very low in July (down

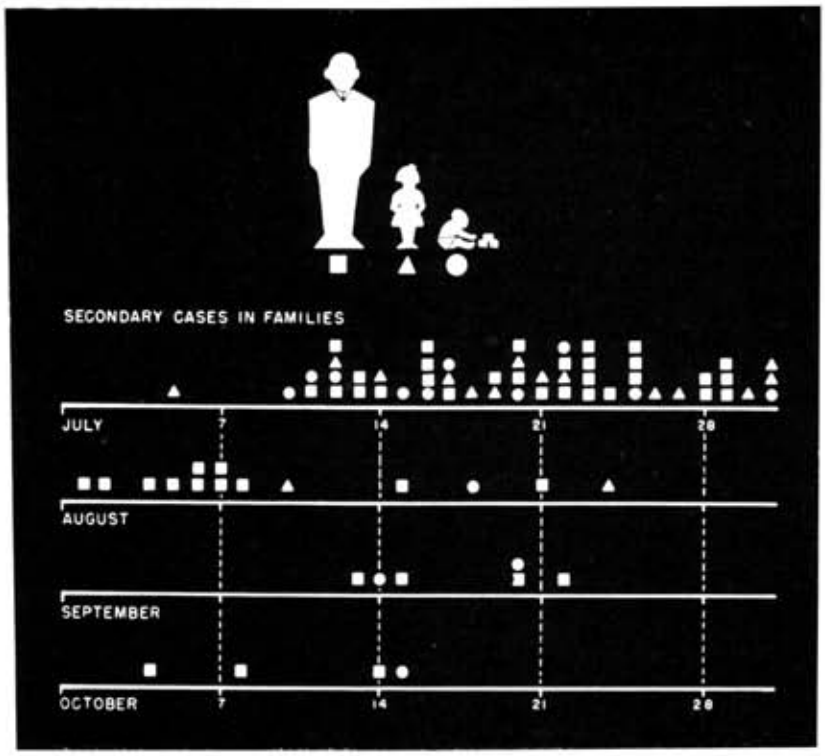


FIG. 4. The time of appearance of secondary cases in family outbreaks. Where two people fell ill at the same time, only one is shown. The key distinguishes adult, school-aged and preschool-aged cases, each square on the figure representing one person.

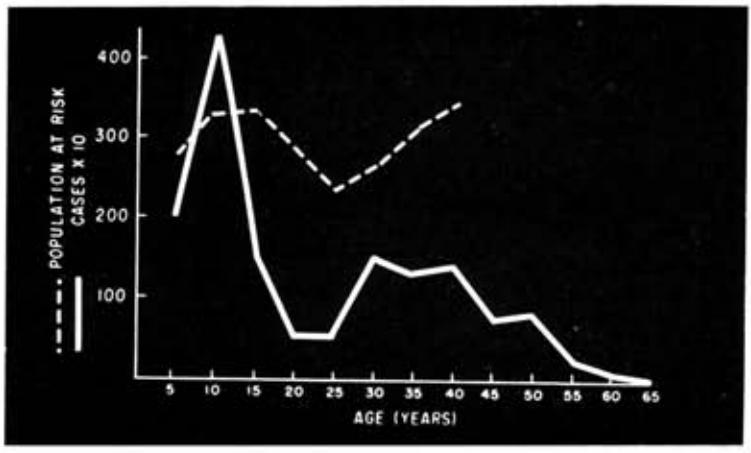


FIG. 5. Age distribution curve of cases and population. The case-age curve is shown by a solid line, the age distribution of the population at risk by a broken line. The practice records were incomplete with respect to the ages of many people over 40 years. (For ease of illustration the number of cases is × 10.)

to 58% in one instance), whereas it was not noticeably affected in the other junior schools or in the senior schools.

The distribution of houses in which cases had been seen was fairly even over the town, despite the rather fragmented nature of the place. The only factor common to the majority was that the children went to the same schools, for although a school served predominantly its own immediate neighborhood, some pupils came from parts of the town remote from it (figures 6–8).

After the children of primary school age, the group next most heavily affected was that aged between 25 and 35 years (figure 9). These were, for the most part, the parents of the schoolchildren.

Clinical Observations

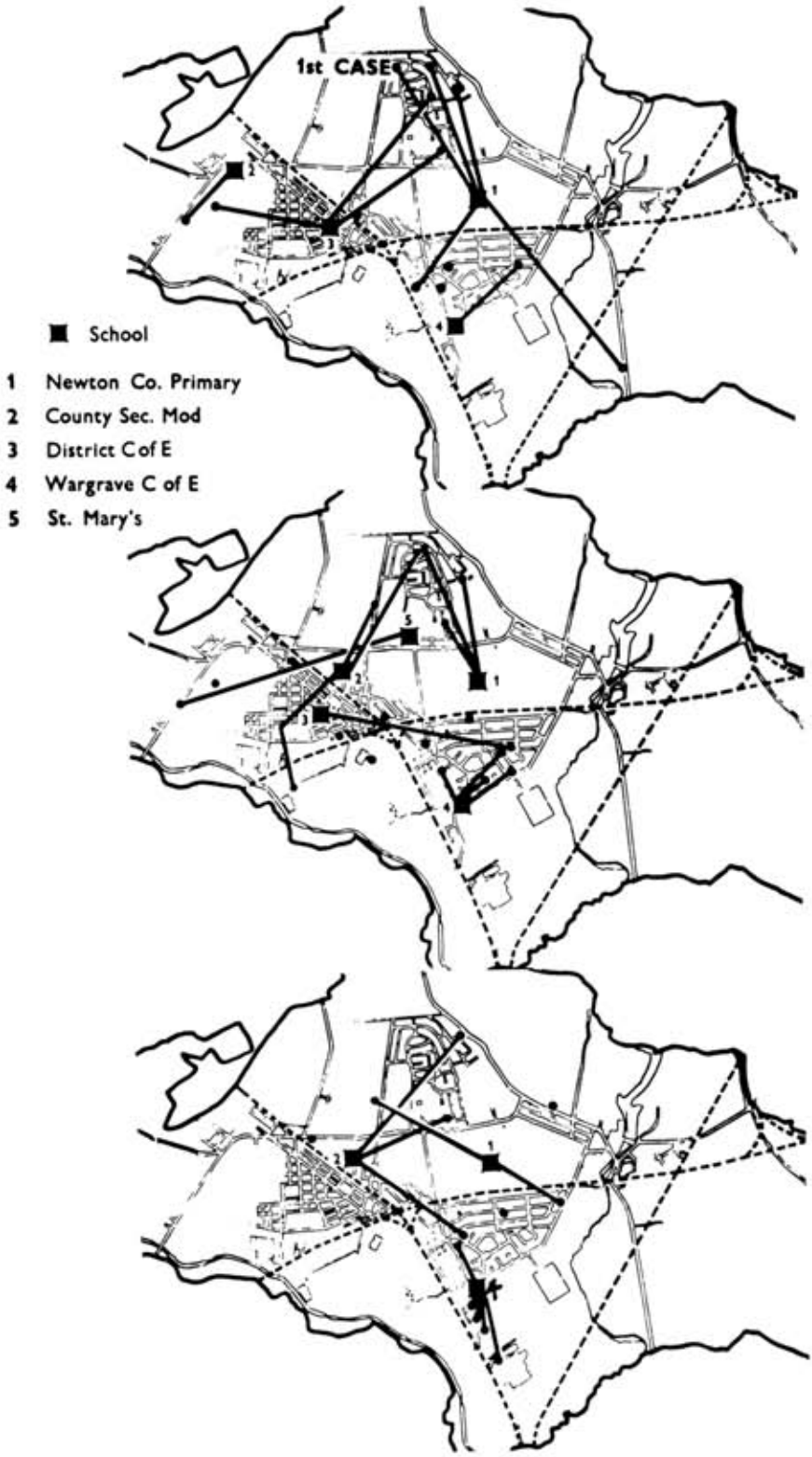
The principal complaint of patients of all ages was of pain, in the head almost invariably, in the limbs or trunk less often. In many instances the headache or limb pain was not very severe, and doubtless a number of people were able to carry on at work and so did not come under observation. Most of the adults with minor degrees of illness came to light only because they were contacts of more florid cases living in the same household.

There were marked differences in the clinical presentation in the adult and in the child. The adult usually had more pain in the limbs, was acutely ill for a longer period, and suffered much more from fatigue and depression in the convalescent phase, but less often developed rash and lymph node enlargement than did the child. In both adult and child there was usually an abrupt onset of frontal and retro-orbital headache, with fever and often vomiting, sometimes preceded by a day or two of vague malaise and lassitude. The headache sometimes first came on during the night, waking the patient from sleep.

After two or three days, headache, limb pain, nausea and fever subsided, and some people rapidly recovered and returned to work within the week. The majority enjoyed a respite for a day or two and then suffered a return of their symptoms, which then persisted for a few more days. Again, some patients recovered rapidly, but others, especially adults, had further relapses or a protracted convalescence.

Pyrexia was of slight to moderate degree, the highest recorded temperature having been 103.2° F., which fell to normal during the first week with the remission of symptoms and rose again with their recurrence. The pulse rate was never very much raised, and was sometimes of the order 50 to 70 beats per minute in the presence of fever. Electrocardiography in 19 of these cases showed only sinus bradycardia, except in two cases that had very slight Q-T prolongation, later tracings being normal.

The disease in its milder forms behaved similarly in children and adults, but the severe adult case presented a picture quite different from that seen in the sick child. In children, the worst type of illness was meningitis without any other signs of involvement of the central nervous system; in the



FIGS. 6 through 8

older patient, there might be encephalitic symptoms in addition to those of meningitic type, accompanied by myalgia of great intensity. The unequal distribution of symptoms and signs between the two age groups (table 3) justifies a classification of the disease into juvenile and adult types.

The Clinical Picture in Children

Headache, anorexia, nausea and sometimes repeated vomiting, slight sore throat and dry cough were the usual symptoms on the first day. A rash was seen in nearly half the cases, and this appeared on the first or second day in the majority (figure 10). It was often fleeting and indistinct, fading and recurring over the course of a week.

Fig. 9. The age/morbidity ratio. The number of cases in each age group, up to the age of 40 years, expressed as a percentage of the total number of people in the sample population.

On the face the eruption was blotchy, macular and dark bluish red, most in evidence on the cheeks. On the chest and back, and less often on the limbs, the appearance was scarlatiniform, although there were sometimes scattered lesions of the facial sort on the trunk also. Round, pink, slightly raised lesions of a centimeter in diameter were sometimes to be seen on the face and trunk, but these were more often found in adults than in children.

A quarter of the children developed neck stiffness on the first or second day, but in half of these the nuchal spasm could be overcome by continued pressure on the occiput. Even true neck rigidity rarely lasted more than four days.

Many had short bouts of colicky abdominal pain, often with slight diarrhea in the first few days, but these symptoms were generally overshadowed by the headache and vomiting, as were the occasional apparently intermittent pains in the limbs experienced by some children.

Figs. 6 through 8. Weekly spot maps, showing the geographic distribution of some of the primary cases and the schools attended by them. Figure 6 (*above*), first week cases; figure 7 (*center*), second week cases; figure 8 (*below*), third week cases.

TABLE 3

Principal Signs and Symptoms

Symptoms	Adults %	Children %	Signs	Adults %	Children %
Headache	90	most	Pyrexia	40	42
Muscle pain	56	6	Rash	9	42
"Neuralgia"	22	—	Lymphadenopathy	30	70
Joint pain	15	8	Conjunctival injection	42	20
Backache	30	4	Faucial suffusion	11	26
Chest pain	15	3	Bradycardia	20	7
Abdominal pain	16	26	Stiff neck	17	24
Anorexia	54	40	Kernig's	17	10
Nausea	24	many	Nystagmus	13	0
Vomiting	25	50	Paresis	7	0
Sore throat	20	18	Tremor	10	0
Cough	15	18	Sensory loss	11	—
Dizziness	25	—	Hyperesthesia	13	—
Drowsiness	18	70	Increased briskness of tendon jerks	13	0
Paresthesia	30	6			
Muscular fatigue	30	—	Sluggish or absent tendon jerks	25	8
Visual disturbance	11	—			
Photophobia	20	13	Babinski's response	6	0
Hyperacusis	13	3	Papilledema	4	0
Rigor	21	6			

No weakness of the limbs was detected in any patient, but transient depression of one or more of the tendon jerks was found in a small group.

About a fifth complained of sore throat, never severe, and a larger number had a bright red suffusion of the pharynx and fauces, sometimes with small palatal vesicles, petechiae or tiny ulcers. Two children at the end of the first week of illness developed clinical and radiologic signs of pneumonitis. One of these children subsequently produced a high titer of antibody to ECHO 9 virus.

Most showed enlargement of the lymph nodes, especially those of the posterior cervical chain, the swelling in many instances becoming palpable

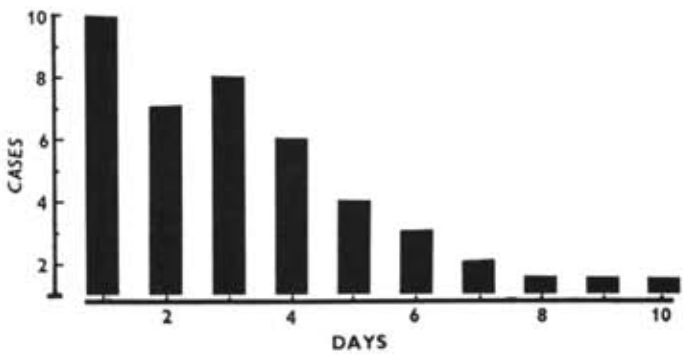


FIG. 10. The day of illness upon which rash was first seen, or was reported to have been first seen.

at about the fifth day. The size of the nodes varied from that of a lentil to that of a cherry stone; the consistency was firm, painless and only occasionally tender. The spleen was not palpably enlarged.

Loss of appetite was rarely persistent. One child became jaundiced in addition to having the more usual symptoms.[6]

The acute stage of the illness, even in the most severe attacks, never lasted more than 10 days, but slight relapses of headache and fever were not uncommon. Schoolteachers observed that a great many of the affected children were long in recovering completely. On returning to school such children were lethargic and inattentive, sometimes for as much as three or four weeks.

The Clinical Picture in Adults

First-day symptoms were much the same in adults as in children, but adults very frequently presented also with conjunctival injection in the form of a leash of engorged vessels running horizontally from the limbus to the inner and outer canthi. This inflammation was painless.

Neck stiffness was much less common than in children, but headache was more intense, occasionally of the greatest severity. In such cases lumbar puncture and the removal of cerebrospinal fluid under pressure gave more relief than did any drug. Violent and repeated vomiting also afflicted some of these people.

In marked contrast to children, the majority of adults suffered in varying degree from pain in the limbs. This usually began on the second day and was sometimes confined to one limb, sometimes was more widespread. Rarely, limb pain was the main source of complaint from the outset, but as a rule headache was the chief symptom in the first few days, limb pain later. At the worst, these pains were very bad indeed, and the few unfortunates who endured these, together with almost intolerable headache, retching, photophobia and hyperacusis, were in a pitiable condition, happily for only two or three days together. As in the children, symptoms tended to remit for a day or two in the middle of the first week.

The limb pain was "deep" in type, and seemed to arise in muscle in most cases. Movement was painful, and in one case subcutaneous edema of the upper limbs was found. There was usually marked tenderness of the painful muscles, and quite often tenderness of muscles in which there was no spontaneous pain. Rest afforded relief, and muscular activity brought on pain which tended to persist for several hours after the exercise which induced it had been discontinued.

In a smaller group, pain was less well localized by the patients and appeared to be segmental. In these, muscle tenderness was less extreme, but paresthesias, usually peripheral, were more common than in the patients with myalgia. The condition of "neuralgic amyotrophy" was closely simulated on three occasions. The "neuralgic" type of pain was often severe and protracted, sometimes accompanied by hyperesthesia over the affected limb,

less often by analgesia to pinprick over small areas of the fingers or toes. Sensory loss was confined to the modalities of superficial pain and thermal sensitivity, and was often late in appearance (never before the end of the first week, and usually in the second or third). In two cases (one of which was myself), more than a year elapsed before sensation returned to the small area affected.

In many cases the tendon jerks were transiently depressed, even lost, in one or more limbs. At other times, in the same people, they were unduly brisk, and, indeed, variation in the activity of the deep reflexes could be observed daily in some cases during the acute phase of illness. Power and "tone" could not easily be assessed at first because of pain, but six adults demonstrated unequivocal weakness, five of these in the second week of illness and one in the sixth week. Three of these were subjected to electromyography and a pattern of partial denervation was found. These patients all made a good recovery.

Some 5% of adults showed signs of neuritis or radiculitis, and it was thought that about 8% had some involvement of the central nervous system. In the acute stage, particularly in those with intense headache, mild confusion, nystagmus, hallucination, drowsiness, blurring of vision, fleeting paresthesias and muscle twitching were to be observed. In a few, positive Babinski's responses and slight papilledema were found.

By the end of the second week, acute pain and fever had subsided in almost everyone, but convalescence was often prolonged by recurrent low grade headache, depression, lethargy by day and sleeplessness by night, irritability and failure of concentration. Of eight people who were still suffering from this melancholy condition in the second month and who were referred for electroencephalography, three were shown to have an excess of slow wave activity of low amplitude and other slight abnormalities of a nonspecific nature. In each case, normal records were obtained three months later, but one patient became depressed enough to need electroconvulsive therapy.

Ready fatiguing of muscle was a striking feature of the disease at all stages, but especially in convalescence, even among people who were not depressed. Characteristically, people got up in the morning feeling well but quickly tired on exertion which, if it was carried on, led to both pain and weakness of the muscles, and consequent feelings of general exhaustion. After sleep, recovery was complete, and the cycle of events was repeated daily.

Electromyography carried out in one of these patients on the thirty-second day of illness showed in the left deltoid "a definite early fatigue pattern, with blurring and broadening of action potentials, on sustained resistance, within 30 seconds." There were gaps in the interference pattern on voluntary effort, but no evidence of denervation, and three months later the patterns were normal.

Several months elapsed before recovery could be said to be complete in many cases. People went to work long before they felt quite well, and it proved impossible to keep all of them under observation, so that one cannot be certain how many were depressed or easily fatigued in the later stages of their illness. There were no deaths, and two years after the outbreak all the patients appear to have recovered (figure 11).

The exigencies of general practice limit the amount of special investigation which can be done, so that the results offered are, regrettably, rather thin.

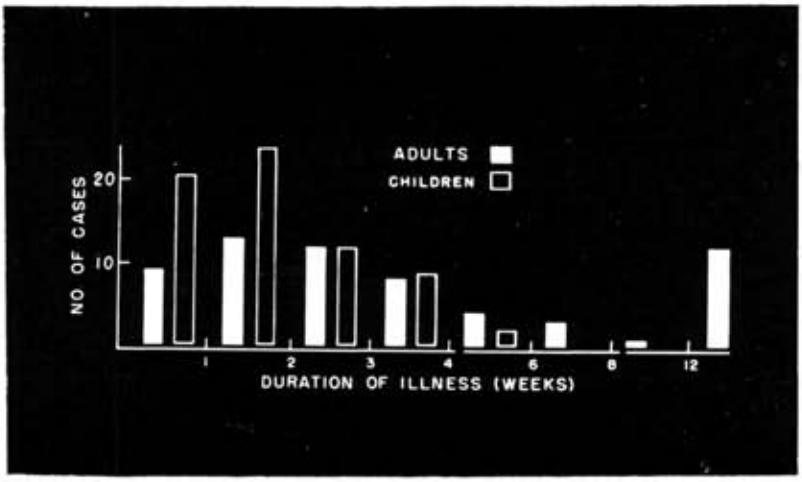


FIG. 11. The duration of illness in children and adults.

LABORATORY INVESTIGATIONS

1. *The Blood Picture.* Total and differential white blood cell counts were carried out in 60 patients on one or more occasions at various stages of their illness within the first five weeks of its onset.

No characteristic picture occurred. Throughout the illness in all cases the total and granulocyte counts remained low normal, except that in the third and fourth weeks a sharp rise in the lymphocyte and monocyte counts took place. Usually there was relative lymphocytosis, never granulocytosis.

Some of the mononuclear cells were abnormal: "These cells are somewhat pleomorphic. The cytoplasm is more basophilic than in the normal lymphocyte and is occasionally vacuolated. The nucleus sometimes shows lobulations and indentations resembling that of the monocyte, and some of the nuclei possess remnants of nucleoli. Occasionally the cytoplasm shows pseudopodia. In size the cells vary from that of a small lymphocyte to that of a large monocyte."

2. *The Cerebrospinal Fluid.* In two adults the fluid was under pressure and contained 860 and 1,250 mononuclear cells per cubic millimeter

and 70 and 100 mg. of protein per 100 ml., respectively. In one child the fluid contained 20 lymphocytes and 45 mg. of protein per 100 ml. All three had signs of meningitis clinically, and lumbar puncture was carried out on the second day in each.

3. *Serology.* Twenty pairs of sera (first and third weeks) were examined for the presence of antibodies to influenza A and B, psittacosis-lymphogranuloma venereum, APC virus, mumps, lymphocytic choriomeningitis, streptococcus MG, *Brucella abortus* and *B. melitensis, Leptospira icterohaemorrhagiae* and *L. canicola,* all with negative results. "Cold" agglutinins were not present, and the Paul-Bunnell test was never positive in a dilution greater than 1/28.

Only nine pairs of sera were available when it became possible to test them against ECHO 9 virus (table 4).

4. *Tissue Culture.* Throat washings and feces collected on dry ice were cultured on HeLa cells, without success in any case. Four fecal specimens

TABLE 4

Titers of Neutralizing Antibody to ECHO 9 Virus Strains in Nine Cases

Haynes Strain		Hill Strain	
Acute Phase Serum	Convalescent Serum	Acute Phase Serum	Convalescent Serum
1 1/512	1/512	5 1/16	1/32
2 1/32	1/128	6 1/128	1/512
3<1/8	1/64	7 1/16	1/256
4 1/32	1/32	8<1/8	1/64
		9 1/64	>1/512

were put up with monkey kidney cells, and strains of virus antigenically identical with the standard Hill strain of ECHO 9 virus were isolated.

DISCUSSION

The central problem posed by the outbreak which has been described, whether or not infection by ECHO 9 virus was the sole cause, cannot be answered with confidence because of the scanty positive results from the virus laboratories. Most observers of other outbreaks of ECHO 9 infection have emphasized the fact that central or peripheral nervous system involvement did not occur. That ECHO viruses can sometimes cause mild muscular paresis is agreed.[3, 9, 5] Tyrrell, Lane, and Snell [12] describe one adult with an encephalitic type of illness which was unquestionably caused by ECHO 9 infection, and these authors also emphasize the variability of the clinical presentation among cases in an epidemic. Muscle pains received little mention in most reports, but were noted in several Belgian outbreaks.[7] Such pains were reported in patients with meningitis caused by ECHO 6 virus infection.[2]

Monophasic, biphasic and triphasic temperature curves like those seen in this outbreak have been seen in many others, such as that reported by Baumann et al.,[1] who also described conjunctival injection among their patients. Lymph gland enlargement seems also to have been a feature of some epidemics [11] but not others.[4, 10]

Some of the many discrepancies to be found between accounts of epidemics occurring in various places may be the result of the situation of the observer. A family physician can perhaps hope to see most of the minor sorts of cases among children, but adults try as a rule to ignore trivial ailments—or what they regard as trivial ailments—in themselves. Of the already selected group of patients who come to see him, the doctor may keep some at home under observation, send others to a fever hospital, and yet others to a general hospital, each with a different provisional diagnosis unless he is able to establish a chain of contact between what appear at first to be clinically dissimilar cases. Observers who do not have entrée into households and work places, or who cannot follow up whole families over a period, are at a great disadvantage, and are likely to gain a wrong impression of the incidence of illness, especially of the less severe sort and of the unusual variants.

The hypothesis that ECHO 9 virus caused the Newton epidemic is based, first, on the fact that ECHO 9 virus was the only agent shown to be present in any of the cases, and second, on the pattern and timing of the outbreak. The types of illness found in Newton have also been reported in epidemics elsewhere in which ECHO 9 virus has been incriminated. Nearly all the cases were seen within the space of 10 weeks in one practice in a small town. Close contact between patients could be established almost invariably without difficulty. The sort of illness seen was always rather unusual, and the author has seen nothing quite like this disorder in its various forms before or since. If this was not one pleomorphic disease, then it must have been several strange diseases which fortuitously fell upon the community simultaneously, in which case the very suggestive chain of contact through junior school children to their families and then neighbors is broken. It seems likely that the epidemic came to an end when it did because spread was person-to-person, and the schools and works and shops closed for the annual town holiday in August, with consequent dispersal of a large part of the populace.

The disease most likely to cause confusion in assessing these cases is poliomyelitis, of which there were two proved cases (virologically confirmed) in the town in August. However, no poliomyelitis strains were isolated from any epidemic case, and the few that had some weakness of a limb had also unequivocal sensory loss which outlasted the weakness. None of the common fevers was prevalent in the town at that time.

The nervous system was certainly affected in some people, and one wonders whether the muscles were sometimes attacked directly, as is known

to occur in Coxsackie B infection. Pain is more often felt in the trunk than in the limbs in Bornholm disease,[13] contrary to what was seen in the present outbreak.

There was quite often slight tenderness of the abdominal wall, maximal sometimes under the right lower rib margin. The liver was never palpably enlarged, but two adults had urobilinogen in the urine for a few days, and four others had thymol turbidity readings of 5 or 6 units (Maclagan) per 100 ml., with slightly raised alkaline phosphatase levels. These investigations were carried out on a group of 16 adults who had continued anorexia and who complained of altered taste of food and tobacco.

The question of whether some people had mild, anicteric hepatitis as part of their illness must, like so many other questions raised by this interesting epidemic, remain unanswered.

Summary

An account is given of an outbreak of disease among the patients of one practice in a small industrial town in Lancashire in the summer of 1956.

The disease presented in several clinical forms, and while some individuals were seriously ill, the majority experienced a disorder of a mild sort. There were no deaths, and the course was usually shorter than two weeks, although a protracted convalescence with relapse of acute symptoms sometimes occurred.

General malaise was in some children accompanied by meningitis, with or without rash and lymphadenopathy. Meningitis also occurred in some adults, often with signs of cerebral irritation, but painful states of the limbs were more common.

The great majority of the patients fell sick in family outbreaks, and the connection between the affected families lay in the schools which the children attended. The disease is believed to have spread first through three primary schools, other schools escaping. The epidemic began to decline from the time the schools closed for the summer holiday.

Infectivity was high, community susceptibility high, incubation short. Transmission was thought to have been by host-to-host transfer.

Evidence incriminating ECHO 9 virus is limited to the isolation of virus in the stools of four patients and the demonstration of a rising titer of neutralizing antibody to the virus in six, all other etiologic investigations having been negative.

Case Reports *

Case 1. A seven year old boy complained first of headache, was hot and drowsy, and voluntarily went to bed. Next day he seemed better and went to school, but in the evening of the fourth day he vomited and complained of headache again, and later of spasmodic abdominal pain. He continued to have headache and abdominal pain next day, and then began to improve again. On the sixth day, and subsequently,

* Brief case reports of 13 individuals in four families were published in an earlier paper.

he was symptom-free, but ran a temperature of 99° F. until the ninth day, and large glands were palpable in the posterior cervical chain and in the axillae.

Ninth day serum: titer of neutralizing antibody to ECHO 9 virus, 1/64.

Twenty-fourth day serum: titer of neutralizing antibody to ECHO 9 virus, 1/512.

Case 2. A five year old girl vomited one evening, but after a restless night seemed quite well. On the third day she was drowsy all day, had a dry cough and nasal obstruction, and vomited once. Next morning she said she had a headache and pain in the right hand. There was a faint erythematous rash on the forearms, and the glands of the posterior cervical chain, axillae and groins were palpably enlarged but painless. Temperature was 100° F; pulse, 120 per minute.

On the fifth day the patient cried a good deal because of headache. She also had pain in the front of the left thigh, both feet and the right hand. Flexure of the neck was painful, but there was no stiffness. She could not, however, kiss her knees. The cough was loose next day, and rhonchi were heard on both sides, but she felt and looked better, and passive flexing of the neck was painless. The patient still had pain in the left thigh, which was tender, and the temperature was 99.8° F. Hitherto there had been no abnormality of the tendon jerks, but now the left knee jerk was sluggish. On the seventh day no abnormalities were detected, and the patient was apyretic, but the lymph glands were still enlarged. She had no further symptoms.

Seventh day serum: titer of neutralizing antibody to ECHO 9 virus, 1/16.

Twenty-seventh day serum: titer of neutralizing antibody to ECHO 9 virus, 1/256.

Case 3. A 27 year old male nurse had as his first symptoms listlessness, nausea, frontal headache with painful ocular movements, and loss of appetite. Pain in the glutei, thighs and left calf began on the second day, when he was seen to have conjunctival and pharyngeal injection, neck stiffness and a temperature of 100° F. (see figure 12). The throat was sore and there was dysphagia, fluids tending to return down the nose. The right side of the soft palate moved less freely than the left, but there was no faucial edema and no exudate. The patient vomited several times on that day and the next, when headache became much more intense, and he began to have pain in the back and fleeting pains in the wrists. There were marked photophobia and hyperacusis, but neurologic signs were made out, the dysphagia having disappeared. On the fourth day the patient felt better generally, with less severe headache, but the pain in the left calf was more troublesome. He continued to improve until the tenth day, but continued to have some headache and pain across the shoulders, although the neck stiffness diminished. On the following day he began to sweat heavily, felt very depressed, and again lost all desire for food, but apart from slight headache had no pain until the eighteenth day, when the shins and back of the right knee felt sore. Two days later the left knee jerk was less brisk than the right, but there was no detectable weakness or sensory impairment. On the twenty-third day the patient was afebrile; erythrocyte sedimentation rate was 13 mm. in one hour (Wintrobe); total white blood cell count, 3,200 per cubic millimeter; polymorphonuclears, 65%; lymphocytes, 31%; monocytes, 3%; eosinophils, 1%. Although the patient complained of pain and weakness of the left leg, no such weakness was detected on examination and electromyography gave normal results.

By the end of the fourth week the patient had greatly improved, but found that he fatigued quickly on taking exercise, especially the left leg. His appetite was poor and he felt depressed, but he returned to work on the thirty-fifth day. When examined three months later he seemed to be normal, but he said that he still had not recovered his former vigor, and that the thigh muscles were stiff in the mornings.

Eighth day serum: titer of neutralizing antibody to ECHO 9 virus 1/8. Twenty-fifth day serum: titer of neutralizing antibody to ECHO 9 virus, 1/64.

Case 4. An eight year old girl complained first of feeling "queer," objected to bright light, sneezed, and vomited twice. She had a restless night and next day was drowsy, had frontal headache, bouts of colicky abdominal pain, shivering attacks, slight cough and repeated vomiting. After another bad night she felt better, having no headache and taking a little food; but the temperature was 101.2° F. and the pulse was 120 per minute, and passive flexion of the neck was painful. There was no neck stiffness or tenderness of muscle, but Kernig's sign was present, more especially on the left. There were no neurologic signs and, although the cough was loose, no signs in the chest. The throat was slightly injected, and the lymph glands of the posterior cervical chain and the axillae were enlarged.

On the fourth day vomiting, drowsiness and irritability returned after the patient had been awakened in the small hours by severe headache. She also had pain above the left iliac crest, nasal congestion and complete anorexia. On the fifth day headache was still severe, and there was pain in the left thigh. Vomiting had ceased, but cough persisted. Neck rigidity was now present, but no other signs of nervous system involvement. The temperature was 102° F. Next day there was some improvement, but chest expansion was reduced on the left, the breath sounds

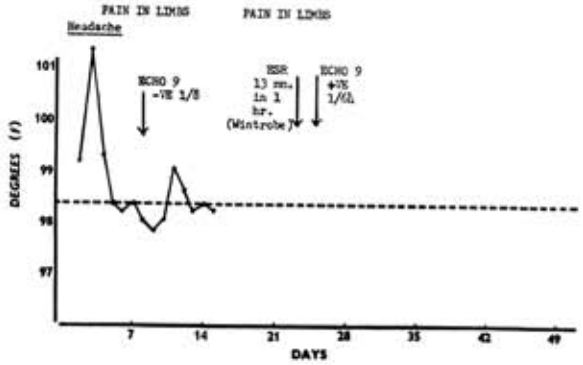


FIG. 12. Temperature chart of case 3.

at the base being of diminished volume. A few rhonchi were audible, and two days later a friction rub was heard in the left axilla. A (portable) radiograph on the ninth day revealed "ill-defined shadowing at the left base." On that day no signs were made out in the chest, there was no neck stiffness, and the general condition was much improved. There was no fever; pulse, 78 per minute; erythrocyte sedimentation rate, 28 mm. in one hour (Wintrobe); white blood cell count, 6,000 per cubic millimeter; polymorphonuclears, 68%; lymphocytes, 26%; eosinophils, 1%; monocytes, 5%.

By the sixteenth day recovery appeared to be complete. The white blood cell count was unchanged except that a few atypical mononuclear cells with bright blue cytoplasm and slightly lobed nuclei were present. The lymph glands were still enlarged a week later, at which time a second radiograph of the chest was normal.

The Paul-Bunnell test was negative, there were no "cold" agglutinins, and no antibodies to streptococcus MG, Q fever, influenza A and B, psittacosis-LGV, *L. icterohaemorrhagiae* and *L. canicola* or lymphocytic choriomeningitis. Fifth-day feces and throat washings produced no growth on HeLa cells.

Fifth day serum: titer of neutralizing antibody to ECHO 9 virus, 1/128.

Sixteenth day serum: titer of neutralizing antibody to ECHO 9 virus, 1/512.

Case 5. An Example of Interfamily Infection (Cases 5–9). A five year old girl was taken by her parents on holiday to the Isle of Man on July 13. With them was the daughter's five year old friend. On July 17 the daughter was drowsy all day and refused food, and next day had a rash on the face which was thought by her mother to be that of rubella. She complained of headache for two days and then rapidly improved, although the rash did not disappear until July 20, when the party returned home. On July 23, when the child was first seen, she seemed to be well, but there was palpable enlargement of the posterior cervical lymph nodes.

Case 6. On her arrival home, the five year old friend of case 5 complained of feeling cold and of a sore throat. Her temperature was 103° F. (figure 13). After a restless night there were still slight cough and sore throat, but no headache. The face was flushed and throat suffused; lymph nodes were enlarged in the posterior triangle of the neck, the axillae and the groins. The patient was generally better

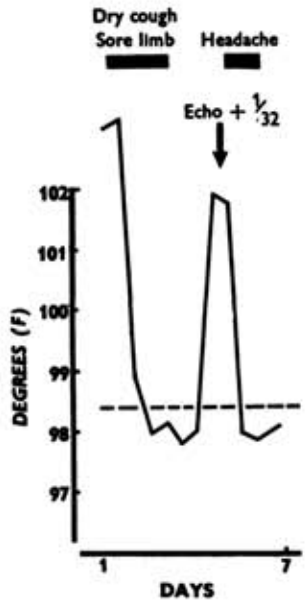


FIG. 13. Temperature chart of case 6.

the next two days and the fever had abated, but on the fifth day, in the early hours, she awoke complaining of headache. The knee jerks were now depressed, whereas earlier they had been as active as the others, but there were no other neurologic signs, and the patient made no complaint about the limbs.

Subsequently she improved rapidly, but for some weeks afterwards was prone to bouts of headache and fever lasting for a day or two. On the nineteenth day she was afebrile. Erythrocyte sedimentation rate, 5 mm. in one hour (Wintrobe); white blood cell count, 4,600 per cubic millimeter; polymorphonuclears, 40%; lymphocytes, 52%; monocytes, 4%; eosinophils, 3%; basophils, 1%.

Fifth day serum: titer of neutralizing antibody to ECHO 9 virus, 1/32.

Nineteenth day serum. titer of neutralizing antibody to ECHO 9 virus, 1/128.

ECHO 9 virus was isolated on monkey kidney cells from third-day feces. There was no growth on HeLa cells.

Case 7. A 36 year old factory inspector fell sick on July 22 while at work. He felt hot and cold by turns, and then had a rigor followed by aching pain, not at first severe, in the shoulders and buttocks. He went to bed and broke into drenching sweats (having taken no aspirin). During the night he had hallucinations, and at 2 a.m. was wakened by intense frontal headache. On the second day he was in a sad state, suffering from unremitting headache of great violence, coupled with equally intense pain in the upper arms, across the shoulders, and in the thighs and calf muscles. He was nauseated but did not vomit. He felt extremely ill, but did not seek medical advice until the fourth day, when he was already much better.

On the sixth day headache returned and the patient was irritable. He had no fever, and the only physical signs to be made out were some enlarged lymph nodes in the axillae. Over the course of the next few days he improved very little, being depressed and unable to concentrate. He tried to do some gardening on the twelfth day but tired very quickly and went to bed early. On the following day he felt too ill to get up. The tendon jerks were all much brisker than they had been, but the plantar responses were normal and the superficial abdominal reflexes preserved. An irregular, ill-sustained nystagmus appeared for the first time on lateral deviation of the eyes, and he found efforts to accommodate painful. The fundi were normal.

Two days later no abnormalities were found on examination. The erythrocyte sedimentation rate and white blood cell counts were normal, and the patient felt rather better, though still depressed and easily tired. He returned to work on the nineteenth day.

The patient was seen subsequently on two occasions, at the end of the second and fourth months, and although there were no physical signs, he said that he did not feel well, having lost interest in his garden and his books. His wife reported that he had become forgetful and untidy where previously he had been meticulous, and, furthermore, that he now fell asleep immediately after his evening meal, behavior quite new to him. He also dragged his right leg slightly. She found the change in his personality to be remarkable. He did not return quite to normal for over a year.

Serum was not tested for the presence of antibodies to ECHO 9 virus, and all other serologic tests gave negative results, including the Paul-Bunnell test, which was carried out on the sixteenth and one hundred thirty-fifth days.

Case 8. A 40 year old minister, father of case 6, began to feel dizzy and to have retro-ocular pain five days after his daughter's return. On the following day he felt unsteady on his legs and dizzy, but had no headache. In the afternoon, pain of some severity was felt deep in the outer part of the left leg, from knee to ankle; there were also fleeting, stabbing pains in the same location, and over the outer aspect of the lower left thigh. The patient went to bed in the evening free of pain, but during the night suffered a return of it. Next morning he still had pain, and the *right* knee and ankle jerks were markedly depressed by comparison with the left, which seemed to be normal. The conjunctivae were injected but he had no fever. There was anorexia, and the patient had lost his enjoyment of tobacco.

On the seventh day, after two days of remission, the patient began to have headache of steadily increasing severity. Neck movement of any sort was painful. He was apyretic and very restless, and would not stay in bed. In the evening there was some lessening of pain, but he was feverish and slightly confused (figure 14). The disc margins were blurred, and the triceps jerks could not be elicited. He looked ill.

Malaise lessened next day, and there was no headache, but the patient now had pain over the sacrum. The tendon jerks were all normal, perhaps slightly overactive. There were no objective sensory changes. There was little change during the following week, headache being almost constant, though not intense, and gluteal pain interfering with the patient's ability to get about. The glutei were tender. He com-

plained a good deal of "muzziness" of the head. By the end of the third week he was feeling much better, and the erythrocyte sedimentation rate and white cell count were normal, but he tired very rapidly if he took exercise.

Easy fatigability, recurrent headache, and aches and pains in the legs continued for about three months, and slight depression, poor appetite, and a constant, disagreeable taste in the mouth for nearly six.

Seventh day serum: titer of neutralizing antibody to ECHO 9 virus, 1/8.

Twentieth day serum: titer of neutralizing antibody to ECHO 9 virus, 1/64.

Case 9. A blotchy rash appeared on the face of an 11 year old boy which lasted for three days. There was no indisposition until two weeks later, when he developed sore throat, headache and rigors. The throat was only slightly suffused, but there

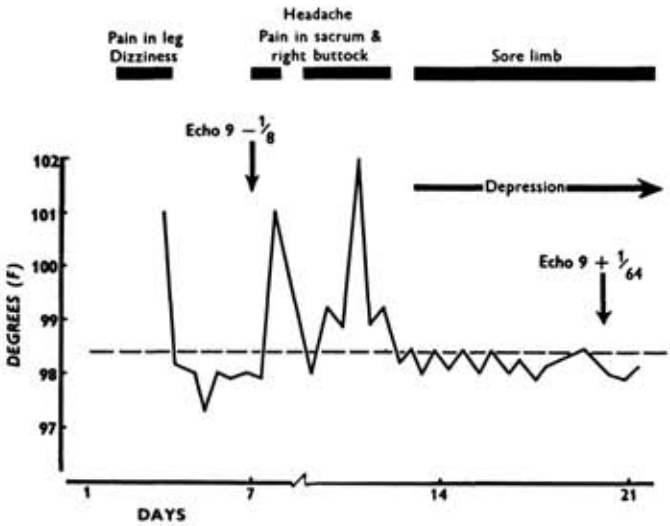


FIG. 14. Temperature chart of case 8.

was marked conjunctival injection, and the posterior cervical lymph nodes were much enlarged. He vomited and was feverish, but within 48 hours felt much better and had no further symptoms.

ACKNOWLEDGMENTS

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My thanks are due also to those of my colleagues in Newton who permitted me to see some of their patients, and to Professor Robert Platt for advice and encouragement from the beginning.

SUMMARIO IN INTERLINGUA

Un morbo infectiose, previemente incognoscite in le communitate, prevaleva durante le tertie quarto de 1956 in le citate de Newton-le-Willows de Lancashire,

Anglaterra. Le morbo se manifestava initialmente in scholares primari e subsequentemente in lor familias. Personas de omne etates esseva susceptibile, e le incidentia del casos secundari intra le mesme familia esseva alte. Le epidemia se propagava in un numero de scholas primari e declinava rapidemente post le clausion del scholas pro le vacantias estival.

Le periodo de incubation esseva usualmente quatro dies. Le periodo del caso individual non esseva determinate.

Le typo e le grado de severitate del morbo variava grandemente, sed le majoritate del casos esseva leve e transiente. Le presentation differeva marcatemente inter patientes pediatric e adulte.

Le patientes pediatric se plangeva de mal de capite e vomito e a vices de dolores in le extremitates. Illes habeva frequentemente un eczema rubelliforme, allargate nodulos lymphatic, e febre e, in certe casos, rigiditate del collo. Illes se sentiva somnolente. In le majoritate del casos, le tertie die videva un melioration, sed isto esseva sequite per un recidiva duo dies plus tarde. Le phase acute del morbo durava rarmente plus que octo dies, sed in le caso del patientes pediatric lethargia persisteva durante plure septimanas.

Le patientes adulte etiam habeva mal de capite, frequentemente de intense severitate, sed in multe casos illes esseva afficite ancora plus per extreme dolores in le extremitates. Eczema esseva pauco commun, sed le presentia de un leve injection conjunctival esseva usual. Myalgia, rapide fatigation muscular, depression, e episodios intermittente de febre afficeva certes del patientes durante multe septimanas post que le phase acute del morbo habeva passate. Un numero non determinate sed considerabile de personas suffreva un forma solmente leve del morbo e continuava travaliar in despecto de illo.

Perdita sensori de grados objective esseva observate in alicun adultos (incluse le autor del presente reporto), e leve grados de paresis muscular esseva confirmate electromyographicamente.

Nulle morte superveniva, e in omne casos le restablimento in le curso del tempore pareva esser complete.

Le observationes continite in le presente reporto esseva facite per un medico private qui habeva solmente multo restringite ressources pro investigationes laboratorial. Le these que le epidemia esseva causate per virus ECHO 9 es supportate exclusivemente per positive constatationes serologic in sex subjectos, con recovration del virus in solmente quatro. Le probas cercante a deteger altere possibile agentes etiologic remaneva uniformemente sin successo. Le conclusion que le epidemia esseva causate per un sol agente es basate super datos clinic e epidemiologic.

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