An epidemic of hand, foot and mouth disease (HFMD) took place throughout Japan in 1978. A total of 36,301 cases were reported and clinical symptoms were mostly typical of HFMD. Most patients were under five years of age. This communication deals with the summarized results of epidemiological information from various laboratories on the incidence of HFMD.

Enterovirus 71 is known to be associated mainly with central nervous system (CNS) diseases in USA (Schmidt et al., 1974; Deibel et al., 1975), Australia (Kennett et al., 1974) and Sweden (Blomberg et al., 1974) and the incidence of HFMD associated with infection by the serotype was only sporadic. In Japan, we experienced a large epidemic of HFMD in 1973. It was the first large-scale epidemic of the disease associated with enterovirus 71 infection in the world (Tagaya and Tachibana, 1975; Hagiwara et al., 1978). Since then, no report has ever been made on such a large-scale outbreak of HFMD associated with enterovirus 71 infection, while epidemics of CNS diseases associated with the serotype were reported from Bulgaria in 1975–76 (Chumakov et al., 1979) and from Hungary in 1978 (Information from the National Institute of Hygiene, Budapest, Hungary, 1978). In Japan, several small outbreaks of HFMD were reported in 1977 from several local laboratories, where enterovirus 71 was isolated from clinical specimens. This was followed by a nation-wide epidemic of the disease in 1978, the second large-scale outbreak of HFMD associated with enterovirus 71 infection. The incidence of disease involving CNS was rather low. This makes a striking contrast to the epidemiology of enterovirus 71 infection in Eastern Europe. We collected epidemiological information from various local virus laboratories on the incidence of HFMD in 1978. This article deals with the summarized results.

* Dr. I. Tagaya, who was the director of the Department of Enteroviruses of this institute, passed away before this epidemiological survey was completed. We remember his remarkable personality and great contributions to public health and virology.
TABLE I

Incidence of hand-foot-mouth disease in 1977 and 1978

<table>
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<tr>
<th>District</th>
<th>1977</th>
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<td>7</td>
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<tr>
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<td>5</td>
<td>7</td>
<td>31</td>
<td>22</td>
<td>14</td>
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<td>9</td>
<td>3</td>
<td>9</td>
<td>15</td>
<td>156</td>
<td>752</td>
<td>936</td>
<td>249</td>
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<tr>
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<td>0</td>
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<td>11</td>
<td>10</td>
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<td>40</td>
<td>627</td>
<td>4591</td>
<td>6244</td>
<td>655</td>
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<td>20</td>
<td>19</td>
<td>50</td>
<td>47</td>
<td>572</td>
<td>3775</td>
<td>4398</td>
<td>470</td>
</tr>
</tbody>
</table>

Total cases reported: 1977—259
1978—36,301

Information was received from 39 of 53 local laboratories, covering almost all parts of the country. No information was obtained from nine prefectures, but eight of them except Okinawa were neighbored by other prefectures where outbreaks of HFMD associated with enterovirus 71 were observed. It is therefore possible that these prefectures also involved the incidence of the disease. In Hokkaido, the northern-most island, many cases of HFMD were observed, but isolation of the virus was not attempted by two laboratories and another laboratory did not succeed in isolating the virus from clinical specimens, probably because of inadequate cell lines used for the test. Therefore, we cannot conclude that HFMD in Hokkaido was also associated with enterovirus 71 infection. In Hokkaido, however, the peak of the incidence of the disease was in July and August, corresponding to the peak of the incidence of HFMD in the neighboring Tohoku Region, where enterovirus 71 was isolated from many cases of HFMD. The movement of people between these two regions, especially during summer time, is so frequent that it may reasonably be presumed that the cases in Hokkaido were also mostly associated with enterovirus 71 infection. Retrospective serological tests with patients' paired sera and/or attempts at isolating the virus from the rest specimens are expected. From other regions or prefectures, enterovirus 71 was isolated from most clinical specimens of HFMD and some aseptic meningitis cases concurrently observed. It is thus concluded that we had a nation-wide prevalence of enterovirus 71 infection in 1978 and the clinical symptoms were mostly of HFMD.

Table I shows the incidence of HFMD reported in 1977 and 1978 by regions. Some of the cases observed in 1977 were diagnosed virologically as being associated with enterovirus 71 infection. Therefore, it seems that the virus was disseminated in various parts of the country during 1977 and HFMD flared up in late spring and summer in 1978. Even in the prefectures where HFMD was reported in 1977, the main outbreaks were observed in 1978. The monthly incidence of HFMD in 1978 by regions is shown in Fig. 1. It is indicated that the epidemic in the south-western parts of the country, Kyushu and Shikoku, took place one month earlier than those in the other regions, the peak of incidence in Kyushu and Shikoku being in June, while that in the other regions being in July. A total of 36,301 cases were reported in 1978 in response to
Fig. 1. Monthly incidence of HFMD in 1978.

Fig. 2. Age distribution of HFMD case in 1973 and 1978.
our inquiries, but the actual number of cases might have been more than 10 times as many as that reported. Figure 2 shows the age distribution of the cases of HFMD in 1978 with the cumulative per cent curve in comparison with the corresponding data in 1973. As can be seen in the figure, most patients were under five years of age in both epidemics, although there was such a slight difference in the age distribution that more younger infants were involved in 1973 than in 1978. More than 80% of reported cases were under six years of age in both epidemics and male patients slightly surpassed female ones (54% versus 46%). Clinical symptoms were mostly typical of HFMD. Concurrent outbreaks of aseptic meningitis were reported from several institutions and symptoms of aseptic meningitis were also observed in a few cases of HFMD. The involvement of CNS, however, in the clinical symptoms associated with enterovirus 71 infection in 1978 was less marked than in 1973. A case each of encephalitis and trochlear nerve paralysis associated with HFMD was reported. They completely cured without any sequelae.
Enterovirus 71 was isolated more efficiently in tissue cultures than in suckling mice as shown in Table II. Various continuous cell lines were used, among which primary African green monkey and cynomolgus monkey kidney cells as well as continuous cell lines derived from them gave higher isolation rates. Various cell strains of the same origin, for example Vero cells, with different passage histories in different laboratories showed variable susceptibilities to enterovirus 71 prevalent in 1978. Human embryo cells were also suitable for the isolation of the serotype. It is of interest that coxsackievirus A-16 was isolated from two cases of HFMD during the period of epidemic of the disease associated with enterovirus 71 infection in one prefecture. In another prefecture a child who contracted HFMD in May 1978 with isolation of enterovirus 71 suffered from similar clinical symptoms in September of the same year. The serological evidence of coxsackievirus A-16 infection was shown after the second disease. These results may indicate that coxsackievirus A-16 was also prevalent in some areas concurrently with the prevalence of enterovirus 71. In western parts of Japan, e.g. in Nagasaki, Fukuoka, Hiroshima, and Tottori prefectures, aseptic meningitis associated with echovirus 6 infection was observed concurrently or near the period of HFMD outbreaks associated with enterovirus 71 infection. In Shimane prefecture adjoining Tottori prefecture, coxsackievirus A-2,6 and B-3 were isolated from exanthematous and herpangina patients, some of whom were diagnosed clinically as HFMD, and enterovirus 71 was isolated later in late summer from other patients with similar clinical symptoms.

Some of the 1978 isolates of enterovirus 71 were examined in our laboratory by the neutralization test with the antiserum to the prototype BrCr strain and that to the Nagoya strain, a representative of 1973 isolates, by the micromethod reported elsewhere (Hagiwara et al., 1978). The BrCr, Nagoya and 258 strains were included in the test. The 258 strain was isolated by Chumakov and his associates (1979) from the brain of a fatal case of enterovirus 71 infection in Bulgaria in 1975. As shown in Table III, our 1978 isolates of enterovirus 71 were not different from Nagoya or 258 strain, but antigenically broader than the prototype BrCr strain. One of the 1978 isolates examined, Yamanashi strain, was less susceptible to both antisera than other isolates.

We acknowledge the courtesy of all who were generous to make their data available for this investigation.

REFERENCES

