HAND, FOOT, AND MOUTH DISEASES

BY

S. R. MEADOW*

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Hand, foot, and mouth disease is being recognized more often, and it is becoming clear that it is mainly a disease of children. The association of mouth ulcers, and vesicles of the feet and hands, with Coxsackie group A viruses has been found in many centres, most often with the A type 16 virus, but sometimes with A types 5 and 10. Because of the mild nature of the disease and its sporadic outbreaks, one observer rarely sees many cases, hence a description of a series of 69 cases seen in general practice may be of value.

Hand, foot, and mouth disease was occurring in many parts of Britain in the second half of 1963: it was reported in Buckinghamshire, Swindon, and Bristol (Crow, Warin, and Wilkinson, 1963), and Aberdeen, Durham, and London (Lipp, 1963; Tattersall, 1963; Meadow, 1963; Abrahams, 1963). In Banbury, Oxfordshire, many cases were appearing. To be certain that these belonged to a clinical entity, complete virology studies would have been needed, whereas only limited virus studies were feasible. Therefore the outbreak was investigated mainly from a clinical and epidemiological approach. From this it became clear that the 69 cases fell into two clinical series, X and Y.

The larger group, series X, consisted of 51 cases originating in one of three outbreaks, and was made up of persons with one or more of the three well-described signs: mouth ulcers, foot vesicles, and hand vesicles. A further group of 18 patients (series Y) had only mouth lesions and these were of a slightly different character from those of series X. At first it seemed likely that series Y had hand, foot, and mouth disease, as infected persons do not necessarily have hand and foot lesions. However, on following up contacts, all cases of series Y could be traced to one of two original sources, but not to any of the 51 cases in the larger series, X. Furthermore the clinical pattern in series Y, and the mouth lesions, were recognizably different from those of

hand, foot, and mouth disease. Series X, the 51 cases of hand, foot, and mouth disease, will be described first.

Hand, Foot, and Mouth Disease (Series X)

Clinical Features. In the Banbury, Oxfordshire, area, there was an epidemic illness during September and October 1963. The illness was mild, only half of the patients consulting a doctor, and ran a course of under 10 days, regressing spontaneously.

AGE INCIDENCE. Amongst 51 cases the age distribution was: 0-5 years, 24; 5-10 years, 10; 10-20 years, 2; 20-40 years, 15.

The small number in the 10-20 years group reflects the fact that the families infected had young children but few members in their teens.

SEX INCIDENCE. There were 30 male and 21 female cases.

MOUTH ULCERS. These were present in all 51 and were often preceded for one or two days by a feeling of malaise, sore throat, and sore mouth. Vesicles appeared, 3-6 mm. in diameter (Fig. 1a), some of them regressing and some bursting rapidly, leaving small shallow oval grey ulcers with a hyperaemic border. In some cases the original vesicles were seen to originate as tiny red macules, and were painful. They occurred in most areas of the mouth except on the posterior pharynx. They were rare on the tonsils and common on the tongue, buccal mucosa, palate, and gums. In 40 cases there were from 1 to 7 ulcers, and 11 had more than 8 ulcers.

HAND LESIONS. In 43 cases there were vesicular lesions which were usually noticed 1 to 2 days after the mouth lesions. They began as red macules (Fig. 1b), gradually becoming vesicular. Some enlarged to form a flaccid superficial blister 3-10 mm. in diameter, containing clear fluid; others remained deeper and smaller. The majority remained oval in shape. They occurred most often on the lateral borders of the proximal phalanges of the fingers and the ulnar borders of the palm. The usual number was two to five, though three small children had a

* Formerly general practitioner, Banbury, Oxfordshire. Present address, Guy's Hospital, London S.E.1.

FIG. 1a.—Ulcers on buccal mucosa of the lower lip.

FIG. 1b.—Small papules on the dorsum of the thumb; a large flaccid blister on the under surface of the second toe was also present.

profuse eruption of tiny palmar blisters. The siting of the blisters seemed related to trauma, blisters being common around rings and on the medial palmar border of those who wrote a lot. They did not irritate and subsided gradually, leaving behind a small red spot.

FOOT LESIONS (Fig. 2a and b). These were present in 17 cases, and uncommon in young children: of 23 children under the age of 3, only 4 had foot lesions. The blisters had the same characteristics as the hand lesions. They were usually present on the toes of women who wore tight shoes; otherwise they tended to be sited on the lateral borders of the feet.

BUTTOCK RASH. This was present in 23 cases, including every recorded case under the age of 3. It

was seen on about the third day of the illness, beginning as a scattered red rash of distinct macules and papules, most of which became vesicles. The vesicular stage lasted a few hours only, until a maculopapular appearance was resumed.

GENERAL SYMPTOMS. There was malaise and marked anorexia in 40 cases. Most of the adults had no general symptoms. There was a pyrexia of up to 101° F. (38.3° C.) in only 3 cases; and the rest were afebrile. When blood counts were done, there was either a normal white cell count or a slight leucocytosis.

OTHER FEATURES. In 30 cases there was redness of the ear-drums, subsiding within 3 days. One housewife had a maculopapular rash of the knees. One child had vesicles on the shoulders.

FIG. 2a and b.—Typical vesicular foot lesions.

SEQUELAE. One girl developed an attack of asthma. There were no other complications. No abnormality was found in 20 cases reviewed 3 months after the illness.

Epidemiology. Banbury is a country town of 20,000 inhabitants in North Oxfordshire. All the cases lived within 5 miles of the town centre. Over a period of two months there were three outbreaks in the area to which all cases could be traced. It was most infectious within individual households, usually occurring in more than half the members, beginning in the young children. In the community as a whole it was not very infectious, and it was seen to affect families on one side of a road and not the other, or only the families whose children played much together. For instance, in one village road of modern semi-detached houses, 6 families out of a row of 7 houses had the illness, while none of those on the other side of the road or farther along it caught the infection.

The disease affected all social classes. The higher incidence of adults (33%) in this series than in the 1957 Toronto outbreak (20%) (Robinson, Doane, and Rhodes, 1958) or the 1959 Birmingham outbreak (12%), described by Alsop, Flewett, and Foster (1960), is probably due only to the closer follow-up of contacts.

The incubation period was 2 to 5 days. As an example of the epidemiological pattern the dates on which individual members of neighbouring families A, B, C, D, E, and F were affected are shown below in Table 1 (*italics* denote adults).

TABLE 1

Date (September 1963)								
1st	2nd	3rd	4th	5th	6th	7th	8th	9th
B B		C C B	F F F D	F A		D	D	A

Virology. Primary isolation was attempted at the Public Health Laboratory, Oxford, in monkey kidney and amnion tissue cultures and by inoculation into newborn mice. Specimens from seven different patients included two specimens of vesicle fluid, two of faeces, and five faucal swabs.

Dr. F. O. MacCallum isolated Cocksackie A 16 virus from one of the specimens, a vesicle on a child's finger. This was isolated in monkey kidney tissue culture. Although primary inoculation into newborn mice failed to yield the virus, the positive tissue culture when inoculated into newborn mice produced typical paralysis. Dr. MacCallum obtained

similar results from a member of the Radcliffe Infirmary staff who caught the illness. The virus isolated from the child was neutralized by a convalescent serum from the Radcliffe patient, who in turn neutralized Cocksackie A 16 virus.

Serological investigations were performed on 5 adults, but the tests were unfortunately very incomplete. The results for Cocksackie A 16 virus were as follows.

Case 1: 4th-day and also 4th-week serum positive at more than 1 : 40

Case 2: 6th-day serum negative at 1 : 10

Case 3: 11th-day serum negative at 1 : 10

Case 4: 12th-day serum positive at 1 : 10

Case 5: 12th-day serum negative at 1 : 10

The results on Cases 2, 3, 4, and 5 are inconclusive because of the absence of tests later than the 12th day. The result in Case 1 is surprising, as it suggests past and not present infection with the virus. This patient had all the clinical manifestations of hand, foot, and mouth disease and had been in contact with other cases.

Course. The disease was self-limiting. Most children were off colour for only 5 days, all were normal within 10 days. Treatment did not affect the duration of the illness.

Mouth Disease (Series Y)

Eighteen cases of an infectious illness with characteristic mouth lesions were seen. Contact with other cases of the disease was common, while there was no apparent contact with any of the cases in series X. These people had a recognizable clinical illness which ran true to type and which differed from hand, foot, and mouth disease and other ulcerative conditions of the mouth in several ways.

It resembled hand, foot, and mouth disease only in its age incidence and incubation period: it differed in that the sufferers were more ill and that half had a fever of 100° to 101° F. (38° C.). No hand, foot, or buttock lesions appeared, and the mouth lesions differed from those of hand, foot, and mouth disease. When starting they looked like Koplik's spots, usually on the buccal mucosa. As the spots enlarged they became ragged grey-yellow ulcers, from two to ten in number. They had a predilection for the fraenum of the tongue and the median raphe of the hard palate. They did not appear on the posterior pharynx nor on the anterior pillar of the fauces. There was no associated gingivitis. In addition to the ulcers, red petechiae were present on the palate, similar to those that are seen in glandular fever. Spontaneous recovery occurred within a week.

Laboratory Investigations. Swabs of the mouth lesions in two patients yielded no virus. Neutralization tests with the sera of one patient showed her to be infected with Coxsackie A 16 virus, serum on the third day being negative at 1 : 10, and in the sixth week positive at more than 1 : 80. Blood counts of 7 patients showed white cell counts between 6,000 and 11,000. Paul Bunnell test on five patients was negative.

The contrasting features of the two types of cases are shown in Table 2.

TABLE 2
FEATURES OF TWO TYPES OF CASES

	Series X	Series Y
No. of cases	51	18
Hand vesicles	85% (43)	None
Foot vesicles	33% (17)	None
Mouth ulcers	100% (51)	100% (18) (starting as 'Koplik's')
Palate petechiae	None	89% (16)
Degree of illness	Mild	Moderate
Fever	5% (3)	50% (9)
Buttock rash	45% (23)	None
Rash elsewhere	4% (2)	None

Discussion

The 51 cases in series X of hand, foot, and mouth disease showed the characteristics of the 24 cases described by Alsop *et al.* (1960) in Birmingham in 1959. In Banbury, Coxsackie A type 16 virus was isolated from a specimen of vesicle fluid: the Birmingham outbreak was also associated with Coxsackie A type 16 virus. Like those cases and in contrast with both the 1957 Toronto disease (Robinson *et al.*, 1958) and the 1959 California outbreak (Magoffin, Jackson, and Lennette, 1961) general symptoms were slight and general body rash absent.

A buttock rash was recorded in 4 of the 24 Birmingham cases and in 4 out of 16 cases seen at a preparatory school in Buckinghamshire (Brown, Wright, and Ogden, 1964). In the present series the buttock rash occurred in each of the 23 cases occurring in children under the age of 3, while foot lesions were rare in this age-group. The site of the vesicles appears to be related to trauma: on hands and feet they develop in areas subject to friction. It is suggested that the buttock rash should be recognized as a feature of hand, foot, and mouth disease in young children.

When the cases of mouth ulceration in series Y presented, it seemed sensible to consider them as variants of hand, foot, and mouth disease, and a watch was kept for the full disease in their contacts. This did not occur and it seemed that this was a different clinical entity (Table 2). Not only was the

natural history and appearance of the mouth ulcers different, but it was epidemiologically distinct. It was a mild infectious illness which could have been a very mild herpetic stomatitis, though there was no apparent herpetic stomatitis prevalent in the area, and it was not associated with gingivitis or adenopathy. Moreover herpes virus is comparatively easy to demonstrate, while the Coxsackie A virus may be more difficult. The lesions of herpangina (Coxsackie A types 2, 4, 5, 6 and 10) are characteristically on the anterior pillar of the fauces and not on the gingival or buccal mucosa, as in this mouth disease.

Full virology and serology studies might have elucidated the problem, but were difficult to arrange in a busy country general practice. However, the one conclusive piece of virological evidence in series Y suggested infection also with Coxsackie A type 16 virus: the series of cases was followed up without any developing peripheral vesicles, so that this finding was unexpected. The different disease picture presumably resulted from an alteration in the virus rather than an alteration in the host. This is possible, for it is becoming apparent that viruses indistinguishable by present techniques may be associated with more than one disease. Coxsackie A type 5 is an example; formerly associated with classical herpangina, it has been isolated from 7 cases of hand, foot, and mouth disease by Flewett, Warin, and Clarke (1963).

A further difficulty is that similar clinical pictures can be produced by different organisms. In particular, the mouth seems very limited in its response to viral infections. Ulcerative mouth lesions occur in many infections including varicella, Echo types 4, 9, and 16, infectious mononucleosis, herpes simplex, and any one of six or more different Coxsackie group A viruses (Bedson, Downie, MacCullum, and Stuart-Harris, 1961). Hand, foot, and mouth disease has now been shown to be associated with three different types of Coxsackie group A viruses: type 16 (Robinson *et al.*, 1958), type 10 (Clarke, Morley and Warin, 1964), and type 5 (Flewett *et al.*, 1963).

It is likely that hand, foot, and mouth disease is more common than its documentation suggests. When a patient presents with a sore throat, the physician does not examine his toes or even his fingers. During the 12 months subsequent to this outbreak 3 further sporadic cases have been encountered in different parts of the country.

Summary

An outbreak of hand, foot, and mouth disease is described, involving 51 cases. In addition to the hand vesicles, foot vesicles, and mouth ulcers, chil-

dren under the age of 3 had a characteristic rash on the buttocks. There was some evidence that Coxsackie A type 16 virus was the causal agent.

A similar though clinically distinct disease is described, characterized by Koplik's type spots leading to mouth ulceration, petechiae on the soft palate, and general illness.

I am grateful to the Public Health Laboratory at Oxford for the virology studies, and in particular to Dr. F. O. MacCallum for the patience with which he received a succession of often inappropriate specimens, and for advice. I thank my former partners in Banbury for bringing cases to my notice. Guy's Hospital Medical School financed the publication of the photographs.

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