OUTBREAK OF 'HAND-FOOT-AND MOUTH' DISEASE IN SINGAPORE

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SYNOPSIS

An outbreak of Hand-Foot-and Mouth Disease (HFM) was discovered in Singapore affecting 104 patients and lasting for $3\frac{1}{2}$ months beginning from late September 1972.

The disease was found mainly in children and young infants of both sexes in the major residential areas of the Republic. Worst hit were Chinese families living in the Housing Board Flats at certain districts like Jurong Town, Queenstown and Lim Chu Kang. Major symptoms and signs found were fever, refusal to take feeds, fretfulness and crying, painful ulcers in the mouth and throat, dysphagia, papular or vesicular rash of the hands, feet, buttocks, knees and other parts of the body. Systemic complications were rare and all recovered spontaneously between the 5th to 10th day. Two patients had a second relapse. Laboratory findings were often unhelpful but the skin biopsy in 4 cases was diagnostic of HFM. A comparison with other western series of this disease revealed a slightly high incidence of oral and cutaneous lesions in the present study. The differential diagnosis is discussed in view of the fact that this viral disease has been previously mislabelled as one of the many local medical conditions.

Coxsackievirus group A, type 16, the agent often responsible for most of the epidemics in the world was isolated from the stool specimen of one patient just before the outbreak died down. The importance of recognising this benign disease is stressed since most local doctors are not aware of the condition.

INTRODUCTION

In 1958, Robinson and his co-workers (Robinson *et al*, 1958) reported an outbreak of 'febrile illness with pharyngeal lesions and exanthem' associated with the excretion of Coxsackievirus A 16 in 60 patients from Toronto. This 'Hand-Foot-and Mouth' disease, (HFM), as is now termed, was characterized by an abrupt onset of fever with prodromal symptoms, painful stomatitis and a skin rash consisting of maculopapular or papulovesicular eruptions of the hands, feet and other parts of the body. Systemic complications were rare. The fever and the orocutaneous lesions spontaneously regressed without residual effect by the 7th day. A few had a second relapse.

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Since then, many such epidemics with similar features and the same causative agent have been reported in many parts of America, Canada, England, Europe and Australia (Magolfin *et al*, 1961; Norton, 1961; Higgins *et al*, 1965; Meadows, 1965; Richardson and Leiboritz, 1965; Hjorth and Kopp, 1966; Evans and Waddington, 1967).

To date, this disease has not been described in Asia including Singapore. The clinical presentation, laboratory findings, differential diagnosis and the management of these cases will be presented and discussed.

MATERIALS AND METHODS

The patients in this study were from many government outpatient dispensaries throughout the Republic, the private clinics and the medical units of the Outram Road General Hospital, Singapore. They were found during the 3rd week of September 1972 to the 2nd week of January 1973 and all the cases had the major clinical criteria of the 'Hand-Foot-and Mouth' Disease (Table I).

Besides the personal data, a detail history was obtained either from the patients or the parents, with special attention to the place of residence, presenting symptoms, previous illness, known contacts, and the course of the illness. After a thorough physical examination including a complete oral inspection, the following investigations

TABLE I

'HAND FOOT-AND MOUTH' DISEASE
(Diagnostic criteria)

PREVALENCE	— Epidemic or sporadic outbreaks
USUAL AGE	— Early childhood
PRODROMAL SYMPTOMS	— 5 to 10 days incubation period with fever, cough, vomiting, malaise, abdominal pain or diarrhoea.
EXANTHEMA	— Common sites are palms, soles, hands, feet, knees, buttock or generalised.
	— Early lesions are discrete reddish maculo-papules 1 to 5 mm. in diameter. Late lesions appear as oval or round pearl-coloured vesicles, surrounded by a narrow zone of erythema running parallel to skin creases. They rarely cause symptoms or rupture and heal with nonscarring brownish stains.
EXANTHEM	— common sites are lips, palate, gums, tongue, pharynx and buccal mucosa
	— Early lesions are small bright petechial-like red spots. Late lesions appear as thin-walled vesicles with a rim of red areola and distributed irregularly in moderate numbers. On spontaneous rupture, multiple painful superficial ulcers are formed.
SYSTEMIC INVOLVEMENT	— very rare. Usually no regional lymphadenopathy.
LABORATORY INVESTIGATIONS	— not helpful except for viral study.
CLINICAL COURSE	— Spontaneous remission within 4 to 7 days.

were carried out: Haemoglobin, total leucocyte count, differential white count, E.S.R., complete urinalysis, throat swabs, blood urea, serum electrolytes and a skin biopsy in selected patients. Virologic study were earlier attempted but were unsuccessful. Subsequently, with the assistance from the Department of Bacteriology, University of Singapore, Coxsackievirus A 16 was isolated and identified from the stool from one patient by the following method:—

Faecal specimen, suspended in Hank's balanced salt solution and antibiotics were clarified by centrifugation at 10,000 rpm. The suspension was inoculated into one-day-old infant mice by the intracerebral and subcutaneous routes as well as into monkey kidney (M.K.) tissue culture. The infant mice were examined on the fifth day for flaccid paralysis and evidence of myositis and typical round cell infiltration in the histological sections of the affected muscles. The tissue cultures were screened for evidence of cytopathgenic effects (CPE) after the 5th day of inoculation. A suspension of the mouse tissue was treated for evidence of C. P. E. in M. K. culture and the tissue culture fluid, for its pathogenicity in infant mice. The infectivity of the tissue culture fluid for the M.K. cells was then examined for its neutralisation with the Coxsackie virus A 16 antiserum.

Management of the cases were largely symptomatic. These include treatment with oral analgesics, sedatives and topical application of bland lotions or local anaesthetic creams to relieve the painful oral ulcers. Soft diet and generous fluid intake were encouraged. The patients were followed up until a remission occurred. Cases that relapsed were restudied and treated.

RESULTS

A total of 104 cases with 'Hand-Foot-and Mouth' disease were found during the $3\frac{1}{2}$ month outbreak in Singapore. The weekly incidence as demonstrated in Fig. 1, rose steeply during September-October 1972 and declined sharply by the end of January 1973.

The districts most affected were the residential areas of Jurong (District 21), Queenstown (District 3) and Lim Chu Kang (District 24) which reported 55, 23 and 11 cases respectively. As illustrated in Fig. 2, other districts in Singapore too, were not exempted. Table II lists the distribution of age, sex, race, types of housing accommodations and affected family members in this series.

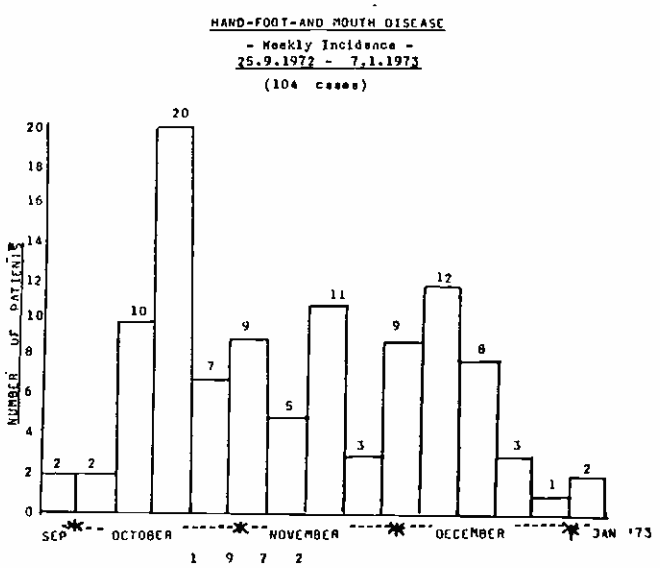

Fig. 1. The weekly incidence of the outbreak from September 1972 to January 1973.

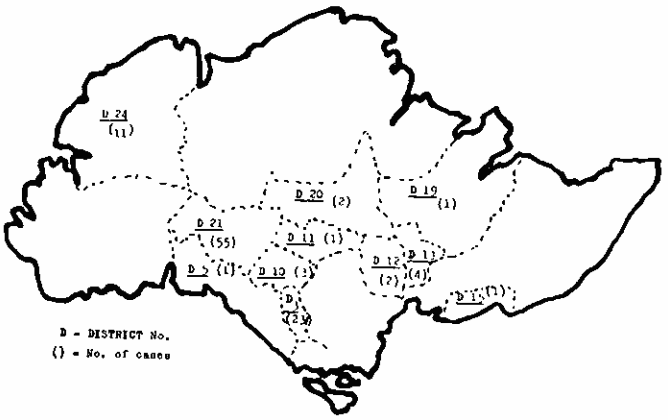

Fig. 2. The distribution of the cases (in brackets) according to the districts in Singapore (D).

TABLE II

HAND, FOOT AND MOUTH DISEASE

(104 cases)

Age Group	Cases	Percentage
Under 1 year	9	8·7
1 to 2 years	26	24·9
2 to 3 years	27	25·9
3 to 4 years	8	7·7
4 to 5 years	12	11·5
5 to 10 years	11	10·6
11 to 20 years	8	7·7
21 to 30 years	2	1·9
Over 30 years	1	0·9
Sex		
Males	55	52·9
Females	49	47·1
Race		
Chinese	95	91·3
Malays	7	6·8
Indians	2	1·9
Housing Accomodations		
Housing Board Flats	87	83·5
Bunglows/Semidetach houses	17	16·5
Number of Families with more than one cases		
Two affected members	13 families	
Three affected members	3 families	
Four affected members	1 family	
TOTAL	17 families	

Ninety per cent of our cases were under the age of 10 and nearly 60% were less than 3 years old. The youngest was 5 months old, and the oldest, 32 years old. There was no significant difference between the sexes. The high Chinese incidence in this series merely reflects the proportion of this racial group in these residential districts. Furthermore, it was found that patients from these residential areas were mainly staying in the close-knit and crowded Housing Board Flats (83·5%) and a total of 17 families were observed to have 2 to 4 affected members, at the same time. In one instance, a number of children were down with HFM disease after attending a birthday party. In another, a doctor and a nurse who contacted the disease from their patients, soon found that their children were similarly affected, thus demonstrating the extreme infectious nature of this viral disease.

TABLE III

HAND-FOOT-AND MOUTH DISEASE
MAJOR SYMPTOMS AND SIGNS
(104 Cases)

Major Symptoms		**Cases**	**Percentage**
Fever		90	86·4%
Refused feeds & vomiting		66	63·4%
Malaise, fretfulness, insomina		55	52·8%
Pain in the mouth or throat		45	43·2%
Dysphagia		31	29·8%
Rash		30	28·8%
Excessive salivation		25	24·0%
Vague headache		17	16·4%
Coryza and cough		17	16·4%
Diarrhoea and vague abdominal pain		3	2·9%
Major Signs			
TEMPERATURE	—99°F to 100°F	73	70·1%
	above 100°F	17	16·4%
EXANTHEM (Mouth lesions)—		104	100·0%
Types	—Petechial maculopapules	22	20·1%
	—Vesicles & Ulcers	82	79·9%
Sites	—Buccal mucosa and palate	90	86·4%
	—Lips and gums	60	57·6%
	—Tongue	31	29·8%
	—Pharynx and tonsils	12	11·5%
EXANTHEM (Skin lesions)			
Hands and Arms	—All types	95	91·2%
	Maculopapules	63	60·5%
	Vesicles	51	49·0%
	Bullae	4	3·8%
Feet and Ankles	—All types	83	79·7%
	Maculopapules	55	52·8%
	Vesicles	30	28·8%
	Bullae	2	1·9%
Buttock	—Maculopapules & vesicles	29	27·8%
Thighs and Knees	—Maculopapules & vesicles	20	19·2%
Generalised	—Vesicles	4	3·8%

The symptoms and signs of the 104 cases are listed in Table III. Prodromal symptoms were common. 90 cases (86·4%) had pyrexia usually mild, between 99° to 100°F, whilst 16·4% developed fever over 100°F. Accompanying pyrexia, were malaise, fretfulness, insomnia (63·4%), headache (16·4%), respiratory symptoms such as coryza or cough (16·4%) and abdominal symptoms such as diarrhoea or vague abdominal pain (2·9%).

Although fever was common in our patients, it was the refusal to take milk feeds, crying, vomiting and fretfulness that caused the parents to seek medical treatment (63·4%). The older children complained of pain in the mouth or throat (43·2%) and some developed dysphagia (29·8%). Excessive salivation in babies was also observed in about a quarter of this series. These symptoms were due to the oral ulcers which were often multiple, widespread and very painful. In two severe cases, the young children were hospitalised because of dehydration from persistent vomiting and refusal to feed. In the majority however, the painful oral lesions caused moderately mild symptoms that cleared up within 4 to 5 days.

Although all patients had skin lesions, yet only 28·8% of them complained of the rash. This was attributed to the mildness of the exanthem which often lacked symptoms such as itch, pain or discomfort. In fact, the parents often thought that the rash was due to mosquito bites! Those with extensive vesicular rash were mistaken for chicken-pox!

Mouth lesions (enanthem) presented in all cases, were found in 3 forms depending on the stage of the disease. Early lesions consisting of petechial maculopapules were found in a fifth of the cases. These developed into small pinpoint vesicles with a thin rim of erythema surrounding each vesicle. Superficial and painful ulcers were rapidly formed when the thin-walled vesicles ruptured and the majority of the patients had this classical lesion when first seen (79·9%.) These ulcers were found irregularly distributed in buccal mucosa, the palate, the lips and gums, the tongue, pharynx and the tonsils in descending order. (Figs. 3, 4, 5 and 6).

Skin lesions (exanthem) were found over the hands and arms in 91·2%, feet and ankles in 79·7%, buttock in 27·8%, thighs in 19·2% and in 3·8%, the rash was generalised. Early lesions consisting of multiple discrete erythematous maculopapules 1—5 mm. in diameter were observed in majority of the patients with hand and feet lesions, 60·5% and 52·8% respectively. The classical lesion of HFM disease is the thick-walled pearl-white, small, roundish vesicle with a zone of erythema and this occurred in large number of the hands and arms (49%), feet (28·8%) and other parts of the body. The palms and sides of fingers

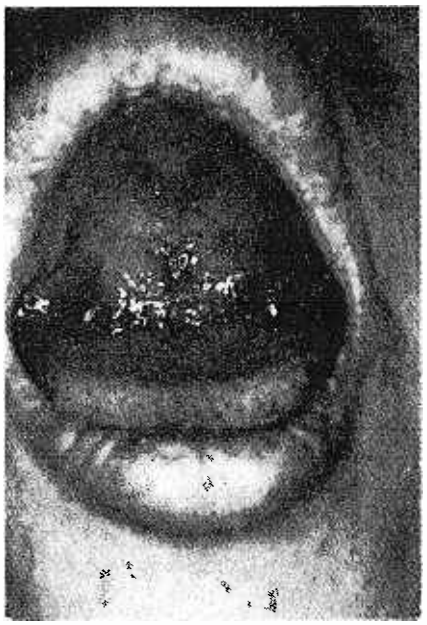

Fig. 3. Classical oral lesions showing petechial-like enanthem on lips, palate and pharynx and shallow ulcers with a zone of erythema on the palate, pharynx and tonsils.

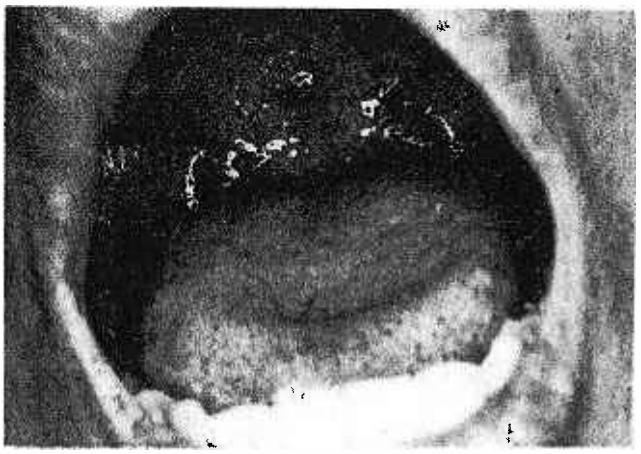

Fig. 4. Multiple vesicles and ulcers with an erythematous zone on the palate and pharyngeal wall.

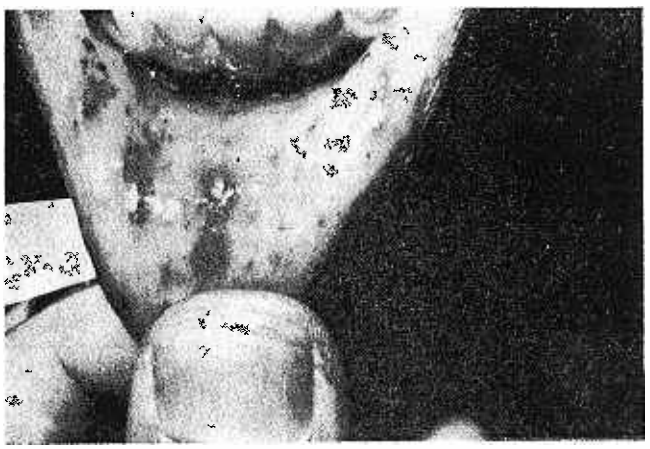

Fig. 5. Brightish red spots, small vesicles and ulcers on the mucosa of the lower lip.

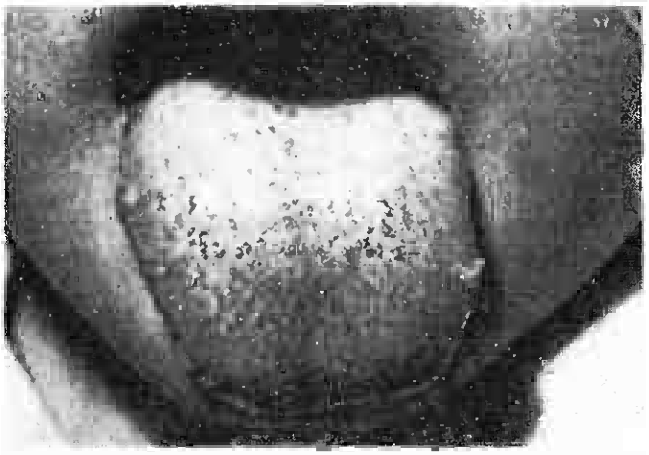

Fig. 6. Multiple small discrete rounded ulcers on the margin of the tongue.

were more affected than the dorsum of the hands. The soles was involved more often than the dorsum of the feet and the extensors of the knees and thighs, more than the flexors (Figs. 7—12). Bullous formation was rare. The vesicular exanthem rarely rupture unless traumatised. They often regressed leaving no scars, but light brownish stains might be found at the old site.s

Fig. 7. Typical lesions on the palm showing numerous small oval to roundish pearl coloured vesicles with a narrow zone of erythema on the palm and fingers of a child.

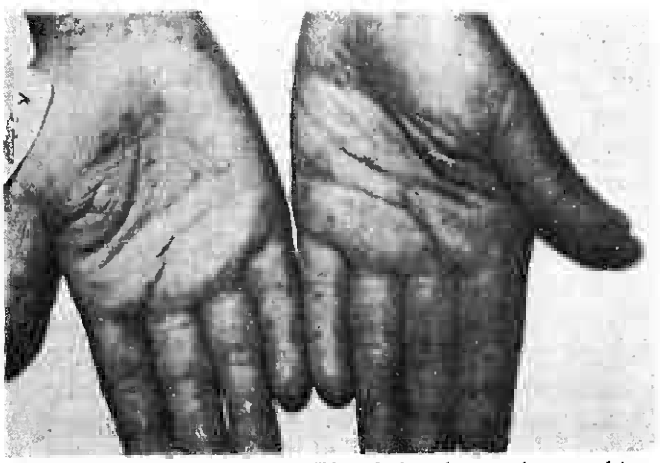

Fig. 8. Similar lesions as Fig. 6, but larger in an older child.

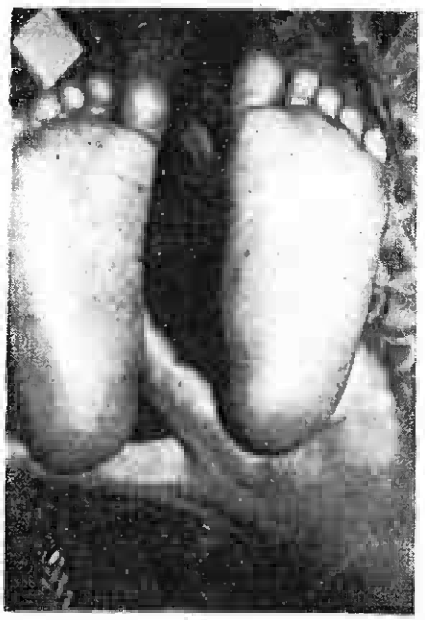

Fig. 9. Early skin lesions on the soles showing multiple discrete reddish macuopapules often mistaken for mosquito bites or dengue haemorrhagic fever rash.

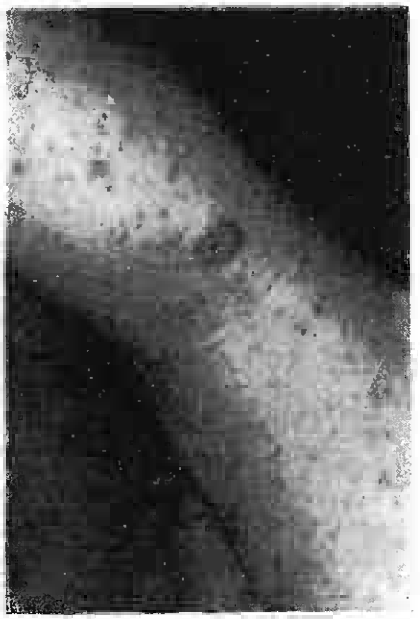

Fig. 10. A bullous lesion amongst the extensive vesicular rash on the ankle and foot.

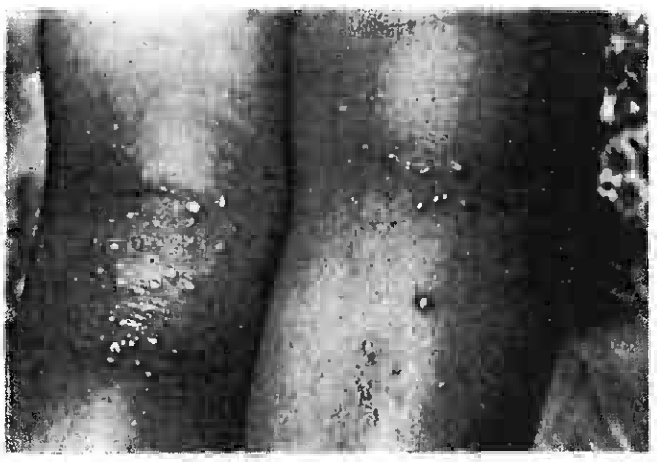

Fig. 11. Typical thick-walled pearl-white vesicles on a red base found on both knees.

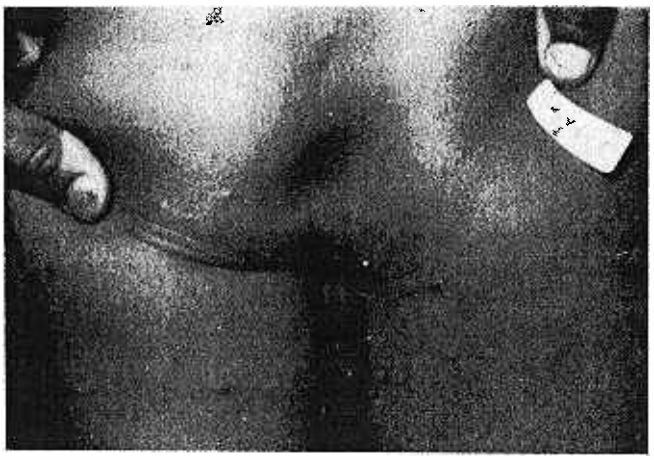

Fig. 12. Vesicular eruptions on the buttock.

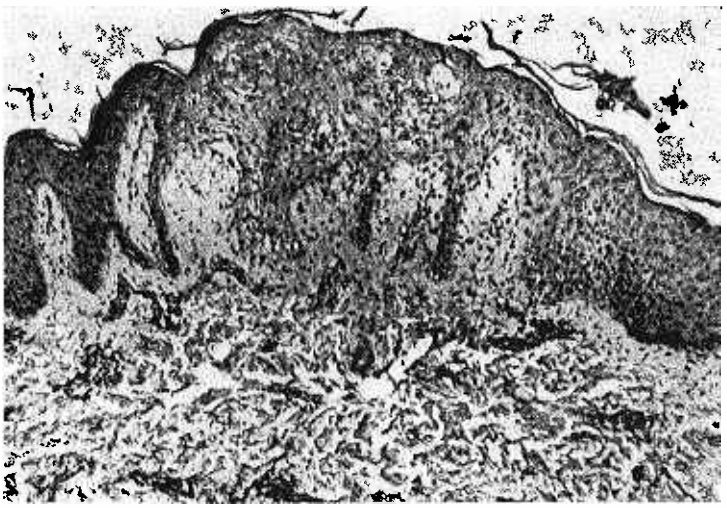

Fig. 13. Histopathology of the skin lesion showing a subepidermal vesicle containing loose strands of fibrin, lymphocytes, moncytes an neutrophils. The overlying epidermis reveals and extensive acantholysis with reticular degeneration. Perivascular foci of lymphocytes and neutrophils were found in the upper dermis (× 75, H & E).

There were few systemic complications. Apart from 2 babies with severe dehydration due to excessive vomiting and required hospital management, 3 had mild bronchitis, 5 transient diarrhoea and 2 were found to have enlarged cervical lymph nodes.

Laboratory investigations were often not helpful. Haemoglobin values were normal (range 11·2—13·5 Gm.%; mean 12·1 Gm.%). Total leucocyte count ranged from 4,800 to 18,700/cu. mm.; mean value of 9,325/cu. mm. Polymorphs were 65% (mean value) and the lymphocytes 28% (mean value). Platelet counts were normal. The ESR were usually normal—ranged from 10 to 26 mm./hr. No abnormalities were detected in the urine, biochemical studies or throat swabs.

Skin biopsy in 4 patients showed the typical histopathology of HFM disease. A subepidermal vesicle containing loose strands of fibrin, lymphocytes, monocytes and neutrophils were seen. The overlying epidermis revealed extensive acantholysis with reticular degeneration. Inclusion bodies and multinucleated giant cells were not seen. In the upper dermis, there was perivascular foci of lymphocytes and neutrophilic leucocytes (Fig. 13).

Although Coxsackievirus A 16 were identified in the stool of one patient, his blood was unfortunately not available for antibody titration. No further material was obtainable for viral study as the epidemic had by then died down.

Simple antipyretics and analgesics such as paracetamol and dispirin were given in most cases with excellent response. Occasional sedation with Benadryl or Phenergan were employed and a few patients also received oral tetracycle as secondary infection was suspected. The painful oral ulcers improved with topical application of diluted Lignocaine cream or Mucaine suspension.

All the patients recovered from the illness between the 3rd to 10th day, and 91 of them (90%) cleared up by the 5th day. Only 5 patients had the disease for 7 to 10 days. Two cases relapsed some 2 to 4 weeks later. The symptoms and signs were milder and the rash cleared up spontaneously by the 5th day.

DISCUSSION

The Hand-Foot-and Mouth Disease (HFM) has not been hitherto known to occur in Singapore and therefore the finding of over a hundred cases over a period of 3½ months in this country is of great interest. Since the disease was first described in 1958 (Robinson *et al*, 1958), almost all the known outbreaks of HFM were confined mainly to the major cities in the western countries (Table IV) Singapore appears to be the first Asian country to report this disease. The rarity of documented cases in Asia is obscure, but amongst other possibilities, it is likely that the disease might have escaped detection. Although the disease was recognized in October 1971 when there was a small outbreak of HFM in some parts of this Republic, a proper study could not be carried out as it disappeared very quickly. Through numerous personal communications with the private practitioners and medical officers in charge of the government outpatient dispensaries in various parts of Singapore and the Peninsular Malaysia, it was confirmed that this disease is in fact, not new to both countries; as such cases have been seen irregularly in their practices for several years. Hitherto, they have all not recognized as HFM. Another reason of the delay of recognition is because the viral disease is mild and self-limiting, therefore, the cases rarely reached the hospital for investigations.

TABLE IV

HAND-FOOT-AND MOUTH DISEASE
PREVIOUS EPIDEMICS

Countries & Cities	Date of Epidemic	Cases Studied	Virus Found	References
Canada				
Toronto	1957	60 cases	CV A 16	Robinson *et al.*, 1958
England				
Birmingham	1959	83 cases	CV A 16	Alsop *et al.*, 1960
Bristol	1960	7 cases	CV A 5	Flewett *et al.*, 1963
Swindon	1962	4 cases	CV A 16	Crow *et al.*, 1963
Bristol	1964	3 cases	CV A 10	Clarke *et al.*, 1964
South Wales	1964	129 cases	CV A 16	Evans *et al.*, 1967
U. S. A.				
California	1959	33 cases	CV A 16	Magoffin *et al.*, 1961
Arizona	1963	21 cases	CV A 16	Richardson *et al.*, 1965
Durham	1966	11 cases	CV A 16 CV B 5 ECHO 9	Miller & Tindall, 1968
Atalanta	1967	40 cases	CV A 16	Froschle *et al.*, 1967
Australia				
Sydney	1961	Few cases	?	Norton 1961; Stewart 1961
Denmark	1966	Few cases	CV A 16	Hjorth *et al.*, 1966
S. Africa	1961/2	Few cases	?	Gear, 1962
Singapore	1972/3	104 cases	CV A 16	Tay *et al.*, 1974

TABLE V

DIFFERENTIAL DIAGNOSIS

FEVER	—	Influenza, upper respiratory infection, gastroenteritis
MOUTH LESIONS	—	Acute pharyngitis, tonsillitis, haemorrhagic dengue fever, leukaemia, blood dyscrasia, drug eruptions, aphthalous ulcers, herpetic gingivostomatitis, herpes simplex, diphtheria, herangina, Behcet's disease, Foot and Mouth disease.
SKIN LESIONS	—	Mosquito bites or insect bites, haemorrhagic fever, allergic drug eruptions, scabies, syphilis, pomphyolx Steven-Johnson syndrome, Chicken pox, napkin dermatitis, pemphigus, dermatitis herptiformis.

A short survey amongst the doctors and the patients' parents yielded a long list of medical conditions for which HFM was mistaken (Table V). During the prodromal period, influenza, upper respiratory tract infection and gastroenteritis were often simulated. When the petechial enanthem appeared, this was often thought to be something sinister eg. haemorrhagic dengue fever, leukaemic deposits, blood dyscrasia, or drug rash (erythema multi-formae). The presence of multiple painful oral vesicles and ulcers usually suggests a long list of differential diagnosis such as aphthatous stomatitis, herpetic gingivostomatitis, herpes simplex or zoster, her-

angina, pyogenic pharyngitis or tonsilitis, diphtheria or the rare Behcet's syndrome. Most of these conditions can be differentiated from HFM because of the lack of the classical skin lesions. The skin lesion (exanthem) have also been confused for a variety of diseases especially when the rash is either too early, too scanty, too profuse or atypical. The erythematous pinpoint maculopapules were often thought by the parents to be mosquito bites, though there was a notable absence of itch. Reddish papules on the buttock may resemble napkin rash and when it was extensive, haemorrhagic fever or allergic vasculitis was diagnosed. The vesicular lesions have also been mislabelled as scabies, pompholyx, syphilis and even varicella. Sometimes, a skin biopsy may be necessary to differentiate HFM from dermatitis herptiformis, bullous pemphigoid, pemphigus vulgaris and Steven-Johnson syndrome especially when the rash is atypical (eg. bullous formation) and in the presence of oral ulcers.

Another confusion arose from another interesting condition which, by strange coincidence, caused an outbreak in Singapore at about the same time as the HFM epidemic. This was the Foot-and Mouth Disease which was found in imported cattle at Jurong (Straits Times, 3rd Feb. 1973). This disease which is due to the RNA virus (a rhinovirus subgroup of the picornaviruses), is very infectious to hoofed animals but may infect men who are in contact with the sick animals. This disease has a similar clinical picture to that of the H.F.M. disease but with some important differences. The patients are often adults who have been exposed to the infected animals or their products. The incubation is short, the fever is high and the vesicular lesions of palms, soles and oropharyngeal mucosa are more extensive. Lymphadenopathy is common finding. Although the disease is self-limiting, high morbidity and mortality have been recorded in children (Flaum, 1939).

The major symptoms and signs in this series do not differ significantly from others reported elsewhere. In comparison to 4 major western series (Table VI), we seem to have a higher incidence of oral lesions, exanthem and fever. 90% of local victims were less than 10 years old and the majority (60%) were under 3 years old. Systemic complications were rare. Only danger in this series was the development of dehydration with associated biochemical disturbances from those patients with persistent vomiting and refusal to oral feeds. Although HFM is generally a benign disease, fatalities had been reported with complications such as meningoencephalitis, myocarditis, bullous erythema multiformae and Kaposi' varicelliform (Wright *et al*, 1963; Goldberg and McAdam, 1963; Gohd and Faigel, 1966; Nahmias and McCroan, 1966). Coxsackievirus A 16 was the responsible agent in these fatal cases. The same virus was also responsible for most of the HFM epidemics in many parts of the world including Singapore (Table IV). Occasionally however, other enteroviruses such as Coxsackievirus A 5, A 10, B 5 and ECHO 9 were found in association with the HFM outbreaks (Flewett *et al*, 1963; Clarke *et al*, 1964; Miller and Tindall, 1968). The rapidity of transmission especially in crowded residential areas and large families as shown in this study is attributed to the spread of the virus by droplets and oral-faecal route. Transmission too may be effected by asymptomatic carriers (Evans and Waddington, 1967).

The fact that this disease usually remits spontaneously by 5 to 7 days after the onset, often helps to differentiate it from other less benign

TABLE VI

HAND-FOOT-AND MOUTH DISEASE
A COMPARISON WITH OTHER EPIDEMICS

	Toronto 1957	Birmingham 1959	California 1959	South Wales 1964	Singapore 1972/3
Total No. cases	60	24	33	129	104
Patients under age 10	78%	87%	75%	90%	90%
Oral lesions	78%	95%	90%	++++	100%
Exanthem	40%	79%	24%	++++	90%
Pyrexia	57%	12%	48%	+++	89%
Sore throat	52%	—	63%	+++	40%
Lymphadenopathy	0	2 cases (12%)	0	+	2 cases (2%)

local conditions. Usually the diagnosis of HFM is easy during an outbreak and when the classical skin and mouth lesions are obvious. However, sporadic cases with atypical enanthem and exanthem may pose difficulties in their diagnosis. These cases may need special investigations like skin biopsy, haematological tests and virologic study to confirm the disease. The importance of recognizing this viral infection is not merely an academic exercise. Knowing it and its natural history will enable one to allay the parent's fear, to withhold unnecessary investigations, and to discourage the exhibition of potentially dangerous drugs eg. wide spectrum antibiotics, as the illness is often self-limiting.

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