during the preparation of the 12-month follow-up programme we observed definite ischaemic changes in the post-exercise electrocardiogram in one of our poor responders—changes which were not present 12 months before. However, one of our original good responders (68%) died after a posterior myocardial infarction in the 12-month interval. Necropsy showed widespread coronary artery atheroma, and on microscopical examination of the thrombus in the right coronary artery it was found that this was probably secondary to haemorrhage into an atheromatous plaque.


## Summary

The resting levels of circulating plasminogen activator, as measured by the euglobulin lysis time, and changes following a standard exercise procedure were studied in 25 male and 25 female healthy middle-aged subjects. There was a significantly higher level in the female group. Comparison with previous results obtained from 50 young healthy subjects aged 18–30 years showed no statistically significant difference between the two age groups. There was evidence to indicate that cigarette smoking may have a deleterious effect on the resting level of circulating plasminogen activator.

The phenomenon of the poor fibrinolytic responder to exercise, previously described in the young subjects, was also shown in the middle-aged population. The middle-aged females had a significantly higher response than the middle-aged males, but there was no significant difference between the total young and middle-aged populations. Cigarette smoking had no influence on the fibrinolytic response to exercise.

A 12-month follow-up study on 18 middle-aged subjects confirmed the phenomenon of a poor fibrinolytic response to exercise.


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# Hand-foot-and-mouth Syndrome in Humans: Coxsackie A10 Infections in New Zealand*

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## Historical

On 19 April 1957 J. H. Seddon (personal communication, 1965) submitted a report to the Research Committee of the New Zealand Council, College of General Practitioners, describing eight cases, in children, of a new clinical illness which has come to be known as hand-foot-and-mouth disease (Alsop *et al.*, 1960). The outbreak occurred in the Mangakino district of the North Island of New Zealand. No virological studies could be done at the time. This original report was later published when the college began issuing a research newsletter (Seddon, 1961). There is evidence, however, that the disease may have been observed many years before this but confused with and taken for the bovine foot-and-mouth disease (Flaum, 1939). In 1958 Robinson *et al.* published the results of an investigation of 60 cases of the same disease which occurred in Toronto, Canada, from late June to early July of 1957. They isolated Coxsackie A16 strains in suckling mice and tissue cultures. Reports of similar outbreaks in other countries throughout 1959, 1960, and 1961 soon followed (Alsop *et al.*, 1960; Magoffin *et al.*, 1961; Stewart, 1961; Flewett *et al.*, 1963). The strain most commonly isolated was Coxsackie A16 (Alsop *et al.*, 1960; Magoffin *et al.*, 1961) but Coxsackie A5 was also isolated (Flewett *et al.*, 1963), the viruses propagating in suckling mice only. Recovery of the latter from one specimen of vesicle fluid added stronger evidence that the disease was of viral origin (Flewett *et al.*, 1963).

In May 1961 the disease was again reported in New Zealand, when 40 cases, mostly children, were seen (Anyon, 1961). Interest was stimulated in this new and interesting syndrome, and throughout 1963 and up until January 1964 numerous outbreaks were reported throughout England and Scotland (Abrahams, 1963; Crow *et al.*, 1963; Fletcher, 1963; Lipp, 1963; Meadow, 1963; Palmer *et al.*, 1963; Tattersall, 1963; Clarke *et al.*, 1964; Erskine and Griffith, 1964; Trowell, 1964). From the limited number of isolations attempted Coxsackie A16 once again appeared to be the strain most prevalent (Higgins *et al.*, 1965), but some Coxsackie A10 strains were also isolated (Clarke *et al.*, 1964). The viruses propagated in suckling mice only.

Outbreaks of the disease also occurred in the U.S.A. in the summer and fall of 1963 (Richardson and Leibovitz, 1965; Cherry and Jahn, 1966). Both articles report the isolation of

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Coxsackie A16 strains from vesicular fluid, adding yet more evidence of the viral aetiology of hand-food-and-mouth disease. These strains were easily isolated in tissue cultures.

The disease was again reported in New Zealand in June 1963, the patient being a boy aged 19 months (Seddon, 1963). A virus was isolated from a faecal specimen when inoculated into suckling mice. The isolate produced myositis and death in the suckling mice. This represented the first virus isolation from the syndrome in New Zealand (Seddon, 1963). In May 1965 a small epidemic occurred in Wellington, in the Wainuiomata district, and specimens were examined for virus content. Strains of Coxsackie A10 virus were isolated, representing the first serological identification of a Coxsackie virus associated with hand-foot-and-mouth disease in that country. The detailed results of this investigation are reported in the present paper. A summary of them in part has been published in another communication (Anyon *et al.*, 1967).

The first New Zealand "isolate" was then re-investigated and identified as Coxsackie A10 (J. H. Seddon, personal communication, 1965).

In 1966 there were outbreaks of the disease in five schools in Cardiff suburbs (Waddington and Evans, 1966). About 800 children and adults were affected. Coxsackie A16 was isolated.

Physicians agree on the clinical manifestations of this syndrome, there being only minor variations. Those who have seen most cases agree that there are two clinically distinct subgroups (Meadow, 1965 ; Waddington and Evans, 1966): either as the generalized form where the lesions occur on the hands, feet, mouth, buttocks, and possibly limbs, or the alternative form where the lesions are confined to the mouth. Gohd and Faigel (1966) reported the case history of a patient whose clinical manifestations resembled those of measles. Recent findings show that infections with Group A Coxsackie viruses are not uniformly mild (Anyon *et al.*, 1967). Evidence to date suggests that Coxsackie A16 virus is associated with epidemics of hand-foot-and-mouth disease, while the other types, A5 and A10 are isolated from sporadic cases.

This human disease is sometimes confused with the foot-and-mouth disease of cattle. The situation has probably arisen because of similarity between the clinical manifestations of the two diseases. It is true that the virus(es) responsible for the disease of bovines is sufficiently similar to the group of human viruses (Coxsackie viruses) to be included with them in the Picornavirus group (small R.N.A. viruses), but there are also marked differences (Andrewes, 1964). The virus(es) of bovine foot-and-mouth disease has only rarely been transmitted to man (Flaum, 1939). In such cases it was possible to passage the virus back into bovines and guinea-pigs. Considering the large numbers of humans who have been in close contact with the bovine virus during large-scale epizootics, the incidence of contact infection is extremely small. In contrast the Coxsackie A strains, particularly Coxsackie A16, causing hand-foot-and-mouth disease in humans are highly communicable and sera from virus positive cases do not contain antibodies which neutralize the bovine virus(es) (Alsop *et al.*, 1960).

## Introduction

The purpose of this communication is to report the virological and serological results of tests carried out on specimens from some patients of a hand-foot-and-mouth disease epidemic which occurred in Wainuiomata, of Wellington province, in May (autumn) 1965. Sera collected from them were tested for neutralizing antibodies against Coxsackie A4 virus and Coxsackie A6 virus as well as Coxsackie A10 virus (isolated from the specimens) because the former two serotypes were repeatedly isolated from Wellington sewage at the time, as was Coxsackie A10 virus (M. F. Duff, unpublished data, 1966). As an extension to this work 203 "normal" sera sampled at random and ranging through varying age groups were screened for antibodies against one of the strains of Coxsackie A10 virus (4004) isolated during this investigation.

## Virus Studies : Materials and Methods

### Isolations

Specimens were received from nine patients belonging to six families (Table I). They were processed, for inoculation into host tissue, by standard methods. Each suckling mouse received approximately 0.03 ml. The various routes of inoculation employed are shown in Table I.

TABLE I.—*Results of Virus Isolations. No Viruses Were Isolated in Tissue Culture, Nor Did the Mouse Isolates Adapt to Growth in Tissue Culture*

| Case | Age | Sex | Specimen | Specimen No. | Date Taken 1965 | Suckling Mice ¶ S/C* | I/P* | S/C+ I/C* | S/C+ I/P* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 5 | M | R/S‡ | 3949 | 17/5 | Not done | Not done | — | Not done |
| | | | P/S† | 3959 | 17/5 | — | — | Not done | Not done |
| 2 | 2 | M | R/S | 3946 | 17/5 | Not done | Not done | A10 | Not done |
| | | | P/S | 3947 | 17/5 | Not done | Not done | — | Not done |
| 3 | 7 | F | R/S | 3953 | 17/5 | A4 | A4 | Not done | Not done |
| | | | P/S | 3952 | 17/5 | Not done | Not done | Not done | A10 |
| 4 | 30 | F | R/S | 3955 | 17/5 | Not done | Not done | Not done | A10 |
| | | | P/S | 3956 | 17/5 | — | — | — | Not done |
| | | | Palm Scrapings | 3958 | 17/5 | Not done | Not done | Not done | — |
| 5 | <2 | F | R/S | 3977 | 18/5 | — | — | — | Not done |
| | | | P/S | 3978 | 18/5 | — | — | Not done | Not done |
| 6 | 3 | M | R/S | 4005 | 19/5 | Not done | Not done | — | — |
| | | | P/S | 4004 | 19/5 | Not done | Not done | A10 | Not done |
| 7 | 1 | F | R/S | 4002 | 19/5 | — | — | — | Not done |
| | | | P/S | 4003 | 19/5 | — | — | — | Not done |
| 8 | 3 | M | R/S | 4624 | 10/6 | Not done | Not done | Not done | — |
| | | | P/S | 4623 | 10/6 | Not done | Not done | Not done | — |
| 9 | 14 | F | R/S | 5425 | 7/7 | — | — | Not done | Not done |
| | | | P/S | 5424 | 7/7 | — | — | Not done | Not done |

*S/C = subcutaneous. I/P = intraperitoneal. I/C = intracerebral. ‡R/S = rectal swab. †P/S = pharyngeal swab. — = no virus isolated. A10 = Coxsackie A10 virus isolated. A4 = Coxsackie A4 virus isolated. ¶ Suckling mice were randomized and redistributed, eight per litter per box. Each specimen was inoculated into two litters. Cases 1, 2, and 3 were from one family, as were also cases 6 and 7.

All specimens were also inoculated, 0.2 ml. being the standard inoculum, into monolayers of primary human kidney cells and H.Ep 2 cells. Mice or tissue cultures which did not show evidence of viral infection were blind-passaged into further mice or tissue cultures. A suspension (blended with chilled fluorocarbon (Arcton 113—Imperial Chemical Industries), followed by centrifugation to achieve some purification) of one of the Coxsackie A10 isolates (4004), was titrated and a limit dilution harvested. This was repeated to obtain a second limit dilution, which was harvested and passaged into a litter to provide a 20% stock bone-muscle virus suspension in standard diluent which was treated twice with fluorocarbon, then ampouled and frozen at −20° C. This "seed" was used in serum neutralization tests and to immunize mice and prepare an immune ascitic fluid. The Coxsackie A4 isolate (3953) was treated in like manner.

### Neutralization Tests

Human sera were screened for neutralizing antibodies to Coxsackie A10 (4004) virus. The sera from the patients were also examined for neutralizing antibodies against Coxsackie A4 (3953) and Coxsackie A6 (isolated from sewage in Wellington) viruses. In all tests the virus dose fell between 32 and 320 mouse $LD_{50}$s. The first dilutions of sera were inactivated for half an hour at 56° C. Initially, they were incubated (for one and a half hours at room temperature) at final dilutions of 1/4 and 1/200. Positive sera were in most cases retested in doubling dilutions until an end-point was reached. The standard inoculum was 0.03 ml. of virus–serum mixture subcutaneously per suckling mouse.

Neutralization tests were performed with mouse anti-Coxsackie A10 (4004) ascitic fluid. A preliminary screening test against several viral antigens—six laboratory prototype strains (all isolated from patients in New Zealand) A1, A2, A6, A8, A10 (63/8396), A23 (E.C.H.O.-9) and A10 (4004)—was performed at a 1/8 final dilution of the immune ascitic fluid, showing cross neutralization with Coxsackie A6. A second experiment was performed at final twofold dilutions from 1/20 to 1/320, followed by final fourfold dilutions from 1/320 to 1/20, 410. Coxsackie strains A6, A10 (63/8396), and A10 (4004) were used as antigens.

## Results

Results are summarized in Tables I–III and in Fig. 1.

Coxsackie A10 virus was reisolated on two subsequent occasions from the rectal swab specimen of Case 4 and reisolated once from the pharyngeal specimen of Case 6. Insufficient material prevented reisolation from the other positive specimens. These A10 strains were neutralized to titre with our stock Coxsackie A10 mouse immune ascitic fluid (immunizing antigen = Coxsackie A10 strain 63/8396) and were also neutralized (at approximately 100 mouse $LD_{50}$s to a titre of 1/200 with our stock Coxsackie A8 immune mouse ascitic fluid (immunizing antigen = Coxsackie A8 strain A805). Our prototype A10 (63/8396) strain did not crossreact in this way, nor did other A10 strains which were isolated from sewage at about the same time.

The immune mouse ascitic fluid prepared against Coxsackie A10 (4004) virus neutralized this virus and the laboratory prototype A10 strain to a titre of 1/5, 120–1/20, 410. Prototype Coxsackie A6 virus was neutralized to a titre of 1/8, but the other five serological types were not neutralized at this dilution.

TABLE II.—*Results of Neutralization Tests with Sera from Seven of the Nine Patients. Serum Was Not Available from Cases 6 and 8. (Coxsackie A10 Virus was Isolated from Case 6). Only Single Sera Were Received from Cases 5 and 7*

| Case | Serum No. | Date Taken 1965 | Serum Titre* Test Virus | | | Coxsackie A10 Virus Isolation (Ref. Table 1) |
|---|---|---|---|---|---|---|
| | | | Coxsackie A10 (4004) | Coxsackie A6 (Sewage Isolate) | Coxsackie A4 (3953) | |
| 1 | 3951 | 17/5 | — | — | 1/600 | — |
| | 5127 | 24/6 | Tr | — | 1/700 | |
| 2 | 3948 | 17/5 | — | — | 1/500 | + |
| | 5128 | 24/6 | — | — | 1/300 | |
| 3 | 3954 | 17/5 | >1/4 | — | 1/400 | + |
| | 5126 | 24/6 | Tr | — | 1/800 | |
| 4 | 4006 | 19/5 | 1/500 | 1/200 | 1/600 | + |
| | 4984 | 21/6 | 1/300 | 1/200 | 1/600 | |
| 5 | 4112 | 24/5 | — | >1/4<1/200 | 1/1800 | — |
| 7 | 5578 | 2/7 | — | 1/4 | 1/600 | — |
| 9 | 5423 | 7/7 | >1/4 | 1/8 | >1/4 <1/200 | — |
| | 6835 | 18/8 | >1/4 | 1/8 | >1/4 <1/200 | |

* Serum titres represent the final serum dilution after addition of virus.
Tr = Traces of neutralizing antibody at 1/4 (25% survival or marked delay in death)
Some sera were not re-titrated, and so the result of preliminary screening dilutions are shown as >1/4< 1/200 representing greater than 50% survival at 1/4 dilution but less than 50% survival at 1/200 dilution, *or* just >1/4 if no mice survived at 1/200 dilution.
Not less than fourfold differences in titre between paired sera from an individual are regarded as significant.

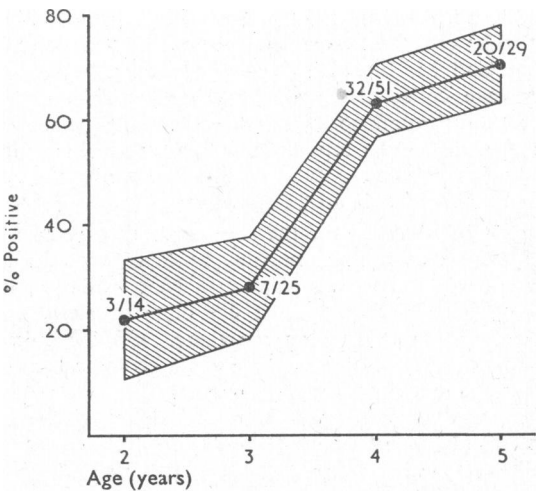
TABLE III.—*Results of Neutralization Tests Using Randomly Collected Sera of Various Age Groups, Coxsackie A10 (4004) Being the Test Virus Antigen*

| Age Group | Total Negative | Total Positive | Positive Titres | | Total |
|---|---|---|---|---|---|
| | | | <1/200 | 1/200+ | |
| 0–5 | 59 | 61 (50%) | 19 | 42 (69%*) | 120 |
| 6–10 | 6 | 10 | 5 | 5 | 16 |
| 11–15 | 0 | 15 | 8 | 7 | 15 |
| 16–20 | 2 | 14 | 8 | 6 | 16 |
| 21+ | 3 | 33 | 18 | 15 | 36 |
| Total (6 and older) | 11 | 72 (87%) | 39 | 33 (46%*) | 83 |

* Expressed as a percentage of the total positive.
The difference between 69% and 46% is significant at level P = 0·005.

## Discussion

Since, of 46 strains of Coxsackie A virus isolated from sewage collected in the Wellington province, 22 strains were identified as Coxsackie A4 (M. F. Duff, unpublished data, 1966) it is not surprising that an A4 virus was isolated from Case 3, and also that the sera from the patients had better neutralizing antibody titres against Coxsackie A4 than against the A6 and A10 viruses. The low antibody titres against the A10 virus are at first sight surprising. It has been reported that herpes simplex virus often does not stimulate antibodies in infants with generalized infections (Szögi and Berge, 1966). Paired sera, taken on 5 August 1963 and 10 October 1963 of the 19-month-old patient from which the first Coxsackie A10 virus was isolated in this country in 1963, contained no complement-fixing antibodies to this virus (J. H. Seddon, personal communication, 1965). There is no information in the literature on neutralization tests carried out on sera from patients in England from which Coxsackie A10 virus was isolated. The more epidemic Coxsackie type A16 virus evidently stimulates fairly high antibody responses (Alsop *et al.*, 1960; Magoffin *et al.*, 1961), likewise the Coxsackie A5 strains (Flewett *et al.*, 1963). High antibody titres may reflect greater virulence of the virus. It is possible that the Coxsackie A10 strains are less virulent and most frequently infect the younger age group who have no neutralizing antibodies in their blood, and that the superficial nature of the infection and the short duration of the disease only result in a very weak primary antibody response. Another probable factor which determines the antibody response is whether or not the patients have been sensitized on a previous occasion to the strain causing the disease (or a cross-reacting strain).




Showing the increase in incidence of contact with Coxsackie A10 virus with age in children of the 0–5 year group: 66% confidence limits are shown. It should be borne in mind that there may be superimposed on the age variation a time variation which may be a variation in host sensitivity or a variation in virus virulence. These experiments have not been designed to differentiate between the two variables.

Consideration of the neutralizing-antibody-positive incidence to Coxsackie A10 in the older groups (Table III) supports the finding of higher titres in the sera of Case 4 (Table II)—the small difference in titre between the two samples could suggest recent active viral activity. It would be interesting to know whether the patients who fall into the clinical subgroup where lesions are confined only to the mouth are patients who have low levels of antibody in their blood and, because of the rapid boosting of their antibody titres owing to the infection, abort the more generalized form of the disease. The results of neutralization tests with "normal" human sera, using Coxsackie A10 as antigen, show that 50% of the population develop neutralizing antibodies by the time they reach 5 years

of age. Gamble (1962) found that the percentage of carriers of enteroviruses in children aged 0–5 years was lowest in the first year of life and highest in the second and third years. One would regard older people with no serum antibodies as likely candidates for infection from these viruses, and often the infection is more severe in such people. A case of hand-foot-and-mouth disease in an 84-year-old woman has recently been described (Waddington and Evans, 1966). She had a chronic infection for two years, and Coxsackie A16 was isolated on several occasions from faeces, throat swabs, and vesicle fluid. One is aware, of course, that this patient may have been seriously debilitated in some way.

Coxsackie A16 has never been isolated in New Zealand. Types A1, A2, A4, A6, A7, A8, A10, A23, and one type which has yet to be identified have been isolated in New Zealand (W. Hamilton and M. F. Duff, unpublished data, 1966). Isolates from sewage collected in the Wellington province from 20 October 1964 through to 21 October 1965 show that Coxsackie A4 was the commonest type in New Zealand during that period (M. F. Duff, unpublished data, 1966). The results of serological tests shown in Table II are in agreement with these findings.

We must be prepared for the time when Coxsackie A16 in a virulent form does appear, possibly by being introduced from another country if it is not already in New Zealand ; it could cause large-scale epidemics as it has done overseas, and may not be as mild as it has been elsewhere. On the other hand, the Coxsackie A10 could be filling an ecological niche and excluding the entry of types A16 and A5. It would be an interesting ecological study to continue isolating viruses from cases of hand-foot-and-mouth disease to see whether results were obtained which supported this hypothesis.

It is to be hoped that areas experiencing large-scale epidemics of this disease will attempt to clarify some of the apparently conflicting results of serological studies.

## Summary

Coxsackie A10 virus strains were isolated from four of nine patients with hand-foot-and-mouth disease. The patients showed no significant serum-neutralizing antibody titre. A survey on "normal" sera showed that 50% of the population develop antibodies to Coxsackie A10 virus by the time they reach 5 years of age.

Various aspects of the epidemiology of, and immunological response to, the Coxsackie A10 virus are discussed, and compared with the properties of Coxsackie A5 and A16 virus strains, which also cause hand-foot-and-mouth disease syndrome.

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