ASEPTIC MENINGITIS IN HONG KONG

BY

D. T. D. HUGHES,* M.A., B.M., B.Ch., B.Sc. M.R.C.P.
Late Captain, R.A.M.C.

J. F. WEBB, M.C., M.D.
Lieutenant-Colonel, R.A.M.C.; British Military Hospital, Hong Kong

W. K. CHANG, M.B., B.S.
Government Virus Unit, University of Hong Kong

AND

R. J. C. HART, M.B., B.S., Dip.Bact.
Major, R.A.M.C.; Royal Army Medical College, Millbank

Small epidemics of aseptic meningitis are not uncommon among British Service personnel and their families in the Far East during the summer months. In 1960 and 1961 two such outbreaks occurred in the colony of Hong Kong, and this paper reports the clinical, epidemiological, and virological findings. A brief account of the first outbreak has already been published (Hart, 1961).

1960 Outbreak

Clinical Picture

The commonest presentation in this outbreak was with headache, fever, vomiting, and a stiff neck, while in many cases the illness also resembled influenza with coryza and generalized aches. Most patients presented signs of "meningism," though five never developed a stiff neck, while three more did so only after 24 hours or more in hospital. These features are shown in Table I,

TABLE I.—*Clinical Features of* 31 *Cases of Aseptic Meningitis in* 1960

Abnormality	No. of Cases	Abnormality	No. of Cases
Fever	30	Abdominal pain	3
Headache	27	Diarrhoea	3
Neck stiffness	23*	Cough	3
Vomiting	18	Tremor	3
Photophobia	13	Febrile convulsion	2
Coryza	11	Disorientation	2
Injected fauces	9	Paraesthesiae in limbs	2
Aching limbs	8	Pleural friction rub	1
Drowsiness	7	Diplopia	1
Palpable spleen	4	Difficulty in micturition	1
Blurring of vision	4	Urinary incontinence	1
Congested fundal veins	4	Bilateral flaccid paresis of legs	1
Pleuritic pain	4	Unilateral „ „ „ „	1

* +3 later.

from which it will also be seen that abnormal neurological signs, apart from those of meningism, were rare. Only two cases showed any paresis, and these recovered completely. In some cases the cervical rigidity had a definite "cogwheel" character. A few had a coarse tremor of hands and tongue. Papilloedema was not encountered, but in several instances the fundal veins were congested. In the majority the disease ran a benign course with complete recovery. Some patients, especially adult women, suffered from persistent headaches, while the tremor remained several weeks with others. As the aetiology was initially uncertain patients were kept in bed and isolated for three weeks, and then slowly mobilized. Some received chloramphenicol or/and sulphadimidine, but there was no evidence that these drugs influenced the course of the illness in any way. Most patients were admitted with a fever of up to 104° F. (40° C.), severe headache and vomiting, and obvious meningism, and would remain acutely ill for two to five days and then recover steadily. Those who were allowed up too quickly often had a recurrence of severe headache and sometimes vomiting and tremor. The children seemed to recuperate more rapidly, and several were apparently normal in every respect within a week. The majority of cases were followed up for 3 to 12 months; recovery was complete in all cases, though prolonged in two, including Case 2, the most serious one.

Case 2.—A woman aged 25 was admitted to hospital with fever, coryza, sore throat, and limb pains. She had returned from holiday in Malaya three weeks previously and had received her third poliomyelitis injection five days before admission. An initial diagnosis of influenza was made, but three days later she developed a severe headache with photophobia, neck stiffness, and drowsiness. She also complained of blurring of vision, and her knee- and ankle-jerks were absent, with mild paresis of both lower limbs. Lumbar puncture yielded clear fluid containing 21 white cells (18 lymphocytes) and 100 mg. of protein. Headache and blurring of vision persisted for over two months and were aggravated whenever she started getting up, while she also became severely depressed. She subsequently developed right-sided pleuritic pain with a loud friction rub, but no abnormality was shown by chest *x*-ray examination. Normal reflexes and power in the lower limbs returned in about three months, but convalescence was prolonged, lasting five months.

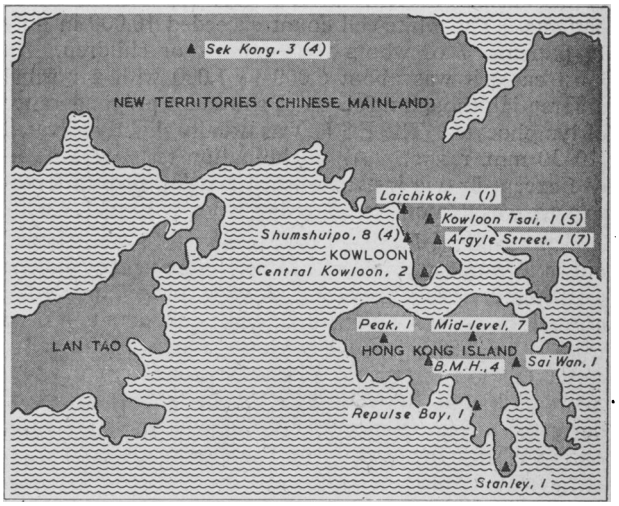
Three of the women were pregnant, and in these the illness affected neither the pregnancy nor the foetus. Infection had started in the second, third, and fourth months respectively in these cases.

Epidemiology

The 31 cases of the 1960 outbreak occurred between April 29 and September 5. All the patients were of European origin. The age/sex distribution is shown in Table II, from which it will be seen that the majority

TABLE II.—*Age and Sex Distribution of Cases in* 1960

Age in Years	No. of Cases	Male	Female
Under 2	3	2	1
2–12	6	3	3
13–20	4	3	1
21–30	15	9	6
Over 30	3	1	2
Total	31	18	13



Sketch map showing distribution of cases in 1960 (31) and in 1961 (21). The 1961 cases are given in parentheses. In 1961 there were no cases on Hong Kong Island.

*Now at The London Hospital.

of cases were in fit young adults, with males predominating. Though cases were fairly well scattered throughout the Colony on both Hong Kong Island (15 cases) and the adjacent Chinese mainland (16 cases), a group of eight occurred in a single block of flats at Jubilee Buildings, Shamshuipo (see Map). Further, all except one of these were in Naval families who were very friendly with each other, and many of whom had had "summer 'flu" with symptoms resembling aseptic meningitis. There were child contacts in most instances, with most Service men living *en famille*. Although in only one instance were members of the same family admitted to hospital, in 10 other cases one or more members of the same family or unit suffered from a "'flu-like" illness at about the same time. Cases 23 and 24 occurred in two brothers, and here aseptic meningitis was suspected in the second brother from the history rather than the clinical findings.

Case 24.—A 12-year-old boy, whose elder brother had already been admitted to hospital with typical aseptic meningitis, developed a fever, with headache and vomiting the next day. When admitted to hospital, two days after his brother, he had a temperature of 99° F. (37.2° C.) but no other abnormal signs and a perfectly supple neck. His C.S.F., however, contained 300 white cells (90% lymphocytes).

Since poliomyelitis among Europeans in Hong Kong often occurred in uninoculated subjects who had recently come to the Colony, the length of stay of these meningitis cases in Hong Kong was ascertained. In fact, 20 cases (65%) had been six months or more in the Colony, so that there was no real evidence that recent arrivals were any more susceptible to the illness. Although poliomyelitis was occurring among the local population only two paralytic cases were admitted to the Military Hospital during 1960, the incidence being low among British Service personnel. Investigation of the status of the present series of cases as regards poliomyelitis inoculation revealed that 16 cases had been fully or partly immunized by Salk vaccine, while 15 had received no immunization. It was interesting that Case 2 presented five days after a third Salk injection. No other case occurred within a month of recent inoculation against poliomyelitis or any other disease.

Laboratory Investigations

Blood.—Full blood counts, Paul–Bunnell tests, and agglutination tests against the typhoid and typhus group of organisms and leptospirosis were carried out on all patients. The white-cell count exceeded 10,000 in only 11 patients, 7 of whom were infants or children. In most cases it was about 6,000 to 7,000 with a normal differential, though a few cases showed a preponderance of lymphocytes. The E.S.R. was usually slightly elevated (20–30 mm. range). All agglutination tests were negative except in one instance, when a rising titre to leptospirosis was demonstrated (rising from 1/10 to 1/1,000).

Cerebrospinal Fluid.—Lumbar puncture was carried out in all cases and twice in some. No constant pattern was found, results covering a wide range and being normal in some. Abnormal white-cell counts varied from 5 to 2,500, but were in the range 5–100 cells/c.mm. in most instances; while the protein content was between 30 and 100 mg./100 ml. in three-quarters of the cases. The degree of C.S.F. abnormality did not correlate with the severity of the illness.

Virology

Wherever possible the following specimens were collected: faeces, C.S.F., throat washings, and paired sera (taken on admission and after two to three weeks). In 1960, unfortunately, a late start was made in collecting specimens, most of which had to be sent back to the Royal Army Medical College in London. A smaller number of specimens were sent to the Hong Kong Government Virus Laboratory and the United States Research Unit at Kuala Lumpur. No deep freeze was available and all specimens were kept in the freezing compartment of the laboratory refrigerator—about −8° F. (−22° C.)—until ready for dispatch to London packed in solid carbon dioxide.

The following was the actual technique of virus isolation.

Faeces.—10% suspensions were made in phosphate-buffered saline containing 100 units of penicillin and 100 μg. of streptomycin/ml. After centrifugation the deposit was discarded and the fluid cultured for bacteria. Bacteriologically sterile fluids were inoculated into suckling mice less than 24 hours old, 0.01 ml. intracerebrally and 0.03 ml. subcutaneously. The mice were observed for three weeks and any sick mice were killed and the brain and torso harvested. These were inoculated into further batches of suckling mice, and those becoming sick between the fourth and seventh days were killed and examined histologically for lesions characteristic of Coxsackie virus infections. 0.1 ml. of the original fluid was also inoculated into each of six tubes of fresh human thyroid-tissue cultures containing 0.4 ml. of Hanks balanced salt solution with 0.5% lact-albumin hydrolysate, 5% calf serum, and antibiotics as above. After half an hour the fluid was removed and replaced by 0.5 ml. of the same maintenance medium. The cells were observed for at least a week for cytopathic effects, and a second passage was carried out before any specimen was reported negative.

C.S.F.—After the addition of antibiotics as above, this was inoculated undiluted into suckling mice and thyroid-tissue cultures, using the same technique except that the maintenance medium in the tissue cultures was not changed after inoculation. Torso extracts from mice whose litter-mates showed lesions characteristic of Coxsackie B infections, and harvests from thyroid-tissue cultures showing cytopathic effects, were inoculated into HeLa-cell cultures for the preparation of high-titre virus suspensions for confirmatory neutralization tests in tissue culture.

Neutralizing Antibody Assay.—Neutralization tests were performed on paired sera from each case simultaneously. Fourfold dilutions beginning at 1 in 4 were prepared. After inactivation at 56° C. for 30 minutes the serum dilutions were mixed with equal volume of stock virus of 100 TCD_{50} per 0.1 ml. and incubated in a water-bath at 37° C. for one hour. Two tubes of monkey-kidney-tissue culture were inoculated with each dilution. Control titrations of the stock virus were put up simultaneously to determine the actual test dosage. Results were read after four days' incubation and expressed as the *reciprocals* of that serum dilution calculated by the Reed–Muench method to protect 50% of the inoculated tissue-culture tubes. In some instances these neutralization tests were carried out in HeLa cells instead of monkey kidney.

Results

The positive results are shown in Table III, from which it will be seen that Coxsackie B1, B4, B5, and poliovirus 1 were incriminated, Coxsackie B4 being the

commonest agent. Two different viruses were isolated from three cases. Serological investigations were incomplete.

TABLE III.—*Positive Virology Results in* 1960

Case No.	Age in Years	Polio Inoc.	Admitted	Virology			
				C.S.F.	Throat Washings	Faeces	Paired Sera
9	6	–	2/6/60	—	—	Polio 1	*No rise in titre to polio 1
11	39	+	10/6/60	—	—	Cox. B1 „ B4	N.T.
14	24	–	13/6/60	—	—	Polio 1	*No rise in titre to polio 1
15	7	+	24/6/60	—	Cox. B4	Cox. B4	Rising titre to Cox.B4 (8 to 128)
16	4	–	25/6/60	—	—	Polio 1 Cox. B4	†Rising titre to polio 1 (4 to 512)
17	27	+	26/6/60	—	—	Cox. B4	N.T.
19	1	+	7/7/60	—	—	Cox. B4	„
20	6/12	–	13/7/60	—	—	Cox. B4	„
21	23	–	22/7/60	Cox. B5	—	—	„
23	14	+	12/8/60	—	—	—	High titre to Cox. B5 in both samples (128)
25	14	+	12/8/60	—	—	Cox. B4	N.T.
28	26	–	30/8/60	Cox. B4	—	—	„
30	1	–	5/9/60	Cox. B5	—	Polio 1	*†No rise in titre to polio 1

* Antibody to poliovirus 1 reached titre of 1/4 only in both specimens.
† Sera tested against poliovirus 1 only.
N.T. = Not tested.

Discussion of 1960 Outbreak

These incomplete results must be interpreted cautiously, but do seem to incriminate Coxsackie B viruses as the main aetiological agents responsible for the outbreak. The role of poliovirus remains uncertain. Only once was it fully incriminated by isolation *and* a significant rise in antibody titre, and even then in association with Coxsackie B4 virus (Case 16). In Case 30, though it was isolated from faeces, there was no demonstrable rise in titre, and Coxsackie B5 virus was found in the C.S.F. This child had a transient flaccid paresis of the right leg, and recovered fully after four weeks.

It was particularly unfortunate that serological tests for poliovirus only, and not against Coxsackie B virus too, were performed on the two cases in which both poliovirus and a Coxsackie virus were isolated. This was because it was possible to isolate poliovirus the more rapidly of the two. Though there have been reports of such double isolations of Coxsackie B and poliovirus (Melnick *et al.*, 1950), there is, in fact, evidence that points to interference between these viruses both in animals and in man. Thus Dalldorf (1951) showed that previous infection by Coxsackie B virus interfered with subsequent poliovirus infection in mice. Several epidemiological studies in man (Dalldorf, 1959) have shown that, while Coxsackie A virus might be associated with poliovirus in cases of paralytic poliomyelitis, Coxsackie B viruses were not commonly found in association with poliovirus at all. Another point against poliovirus playing a major part in causing this outbreak of aseptic meningitis was the low incidence of paralytic poliomyelitis among the same population at risk, although many of them were uninoculated. If poliovirus were indeed responsible for an appreciable number of cases of aseptic meningitis a much higher incidence of paralytic poliomyelitis would have been expected. In relation to the two cases of apparent dual infection it is interesting to speculate whether the Coxsackie B4 virus found in Case 16 may have modified the poliovirus infection so that it produced an aseptic meningitis rather than paralytic poliomyelitis.

1961 Outbreak

Clinical and Laboratory Findings

The clinical features and the abnormalities in the blood and cerebrospinal fluid were similar to those in the 1960 outbreak, with a few differences. Rash occurred in three cases, being morbilliform in nature but confined to the face and upper trunk. Lesions of the soft palate and buccal mucosa occurred in two patients, both of whom had a rash. The oral lesions consisted of petechiae on the palate associated with small shallow ulcers of the mucosa up to about 3 mm. in diameter. Conjunctivitis occurred in two cases, neither with a rash or oral lesions. An almost biphasic illness occurred in two patients with interim periods of four weeks and two days respectively.

Case 5.—A 9-year-old boy was admitted to hospital with a 24-hour history of severe frontal headache and fever. Closer questioning revealed that he had been having headache for the previous month, and had had an episode of fever four weeks previously which his parents had regarded as influenza. He had only minimal neck stiffness and his cerebrospinal fluid was normal.

Case 11.—A 9-year-old boy had a 24-hour history of fever, headache, drowsiness, and limb pains. On examination he was ill and toxic-looking, with a temperature of 104° F. (40° C.), reddened fauces, and a very stiff neck. Lumbar puncture yielded clear fluid containing only 3 white cells and 20 mg. of protein. His condition improved rapidly over the first 48 hours and his temperature fell to normal by the third day. On the fifth day he produced a second spike of fever, up to 101° F. (38.3° C.), associated with severe headache and the appearance of a morbilliform rash confined to the face. He also developed a few petechiae on the sofe palate and small ulcers of the buccal mucous membrane. The rash faded and he recovered steadily over the next five days.

Epidemiology

In 1961 the majority of cases occurred between June 23 and August 12, during which time there were 21 cases, mostly in children under 12 years (18 out of 21). The endemic period coincided with the peak of incidence of poliomyelitis in the Colony, which was greater among Service personnel than in 1960. The distribution of cases (see Map) showed that, in contrast to the preceding year, all cases were from the mainland (Kowloon and the New Territories). The cases occurred mostly in four particular areas—Argyle Street, Kowloon Tsai, Shamshuipo, and Sek Kong. These areas were densely inhabited by the Chinese community, among whom non-polio enteriviruses are widely distributed. A high incidence of Coxsackie B4 and A9 viruses has been reported in Chinese children in these areas (Chang and Shum, 1962), although aseptic meningitis caused by this virus has not been described. Familial aggregation was again observed during this outbreak ; two pairs of sibs (Cases 12 and 13 ; Cases 16 and 17) and a mother and a daughter (Cases 19 and 8) being among the series. All except Cases 11 and 19 had been immunized against polio with Salk vaccine, while Case 21 had had a severe attack 10 years previously. The development of the illness in the families and contacts suggested that the incubation period might vary from 2 to 14 days.

Virology

In 1961 similar specimens were studied locally at the Hong Kong Government Virus Laboratory. Examina-

tions were carried out as soon as possible after collection, using the techniques already described with some modifications. Monkey-kidney tissue was used as a medium for growth and in which to observe cytopathic changes. Each cytopathic agent recovered was identified by neutralization tests in tissue culture using batteries of known antisera to poliovirus types 1–3, Coxsackie A7 and A9, and Coxsackie B1–B5. Ancillary tests were also carried out on the sera of four chosen cases for comparison of antibody titre for prototype Coxsackie A9 virus and patients' viruses.

Results

Of the 21 cases investigated, Coxsackie A9 virus was recovered from 15, in 11 instances from faeces, 9 from C.S.F., and 3 from throat swabs. This gives a virus recovery rate of about 50% for faeces and C.S.F. Virus was isolated from C.S.F. collected two to eight days after the onset and from faeces as early as the first day and as late as the fifteenth. Neutralization tests were carried out on paired sera in 19 cases, 7 of which showed a fourfold or more increase in antibody titre. Taking the isolation and neutralization tests in conjunction, Coxsackie A9 virus was incriminated in 19 out of 21 cases (see Table IV). Poliovirus 1 was isolated from the faeces of two patients; one of these exhibited Coxsackie A9 virus in the C.S.F., while the other showed an increase of antibody titre against Coxsackie A9 virus.

The findings of ancillary tests, shown in Table V, indicated the similarity of antibody response of the patients to Coxsackie A9 virus, Dalldorf strain, and the viruses isolated from the patients themselves.

TABLE IV.—*Result of Virus Isolation and Serological Tests in 1961*

Case No.	Sex and Age	Date of Onset	Virus Isolation			Neutralizing Antibody		
			Specimen	Day	Result	Day	Titre (A9)	Polio 1
1	F 8	23/6/61	C.S.F.	2	Cox. A9	3	<4	—
			T/swab	3	,, ,,	19	8	—
			Faeces	7	,, ,,			
2	F 4	24/6/61	C.S.F.	2	Neg.	3	4	501
			T/swab	3	,,	20	16	501
			Faeces	7	Polio 1	136	16	—
3	M 6	1/7/61	C.S.F.	2	Cox A9.	11	16	1,024
			T/swab	4	Neg.	29	16	1,024
			Faeces	4	Polio 1			
4	M 21	3/7/61	T/swab	5	Cox. A9	2	<4	—
			Faeces	6	Neg.	8	<4	—
5	M 9	7/7/61	C.S.F.	33	Neg.	33	256	—
			T/swab	34	,,	52	4,096	—
			Faeces	37	,,			
6	M 9	10/7/61	T swab	10	Neg.	3	16	—
			Faeces	15	Cox. A9	20	32	—
7	M 7	13/7/61	C.S.F.	4	Cox. A9	4	64	—
			T/swab	6	Neg.	16	64	—
			Faeces	9	Cox. A9			
8	F 7	20/7/61	C.S.F.	8	Cox. A9	12	8	—
			T'swab	8	Neg.	20	8	—
			Faeces	1	Cox. A9	108	8	—
9	F 10	21/7/61	C.S.F.	3	Cox. A9	2	16	—
			T/swab	7	Neg.	13	16	—
			Faeces	6	Cox. A9			
10	F 3	21/7/61	C.S.F.	2	Cox. A9	11	64	—
			T'swab	7	Neg.	25	128	—
			Faeces	11	,,			
11	M 9	30/7/61	T/swab	3	Neg.	4	16	—
			Faeces	3	Cox. A9	19	128	—
12	M 6	4/8/61	C.S.F.	2	Cox. A9	2	<4	—
			T/swab	3	,, ,,	14	16	—
13	F 3	5/8/61	C.S.F.	11	Neg.	13	64	—
			T'swab	12	,,	27	64	—
			Faeces	15	Cox. A9			
14	M 6	6/8/61	C.S.F.	5	Cox. A9	15	128	—
			T/swab	6	Neg.			
			Faeces	9	Cox. A9			
15	F 8	6/8/61	C.S.F.	4	Neg.			
			T/swab	5	,,			
			Faeces	9	,,			
16	M 7	6/8/61	C.S.F.	6	Neg.	6	64	—
			T'swab	6	,,	24	128	—
			Faeces	13	,,			
17	M 5	7/8/61	C.S.F.	5	Neg.	13	256	—
			Faeces	12	Cox. A9	23	1,995	—
18	M 2	7/8/61	C.S.F.	4	Neg.	4	<4	—
			Faeces	11	,,	25	256	—
19	F 34	9/8/61	C.S.F.	5	Neg.	11	8	—
			Faeces	5	,,	21	8	—
20	F 6	12/8/61	C.S.F.	2	Cox. A9	10	64	—
			Faeces	11	,, ,,	21	128	—
21	F 35	12/8/61	C.S.F.	2	Neg.	8	<4	—
			T'swab	3	,,	19	<4	—
			Faeces	6	Cox. A9	70	64	—

TABLE V.—*Patients' Serum titre for Prototype Coxsackie A9 Virus and Patients' Virus*

Case No.	Prototype Virus			Homologous Virus		
	Strain	Virus Titre	Antibody Titre	Source	Virus Titre	Antibody Titre
10	Dalldorf 50546	$10^{-6.8}$	126	C.S.F.	$10^{-6.7}$	256
11			126	Faeces	$10^{-6.7}$	126
17			1,995	,,	$10^{-6.3}$	1,995
20			126	C.S.F.	$10^{-6.3}$	126

Discussion of 1961 Outbreak

Although there have been several reports of aseptic meningitis caused by Coxsackie B viruses and certain types of E.C.H.O. virus (Girardi *et al.*, 1957; Rhodes and Beales, 1957; Syverton *et al.*, 1957; Melnick, 1957a; Barron *et al.*, 1958), claims for an aetiological role of Coxsackie A9 virus for this disease have been few. Melnick (1957b) mentioned two cases in which Coxsackie A9 virus was recovered from the cerebrospinal fluid, while we can find five other reports of its being isolated from the faeces of patients with aseptic meningitis (Grist *et al.*, 1960; Lerner *et al.*, 1960a, 1960b; Stern, 1961; Combined Scottish Study, 1961).

The first report of Lerner *et al.* (1960b) concerns 15 cases of Coxsackie A9 infection in Boston children during the months of July to October, 1959. The predominant clinical features were fever, sore throat, skin rashes (maculopapular, petechial, and vesicular), and pneumonia. This was the first description of vesicular rash and pneumonia associated with infection by this virus, and one of the pneumonic cases was fatal. There were four instances of aseptic meningitis, only one with neck stiffness. The second paper (Lerner *et al.*, 1960a) refers to a small outbreak (seven cases) arising in a laboratory and spreading among the workers in the laboratory and their families. The spread was such as to suggest an incubation period of from 2 to 12 days. Those reports are of interest in pointing out the widespread spectrum of disease produced by the virus and suggesting a possible incubation period. Though many of our patients had coryza and sore throat with injected fauces, none had pneumonia or vesicular rash. A similar incubation period was suggested from our study.

In the 1961 outbreak Cocksackie A9 virus was found to be the aetiological agent, evident by the isolation of the viruses from cerebrospinal fluid, the demonstration of rising antibody titre in patients, and the similarity of antibody titre for the prototype virus and homologous viruses. The isolation rate of Coxsackie A9 virus from cerebrospinal fluid was relatively high and could be compared with that of faeces. Only the recovery of the virus in cerebrospinal fluid can furnish an early conclusive diagnosis, especially in places where enteroviruses are heavily distributed, for dual infections can be common in poliomyelitis endemic areas

(Melnick *et al.*, 1951). The importance of serological tests in addition to viral isolation is shown. In Case 2, that of a girl who had been inoculated against poliomyelitis with Salk vaccine and who showed the presence of poliovirus type 1 in her faeces and a high titre of polio antibody in her blood, a definite fourfold rise of antibody against Coxsackie A9 virus was demonstrated. The case might have been missed or misinterpreted if Coxsackie A9 virus infection had not been suspected. In Case 3 (also immunized against polio) Coxsackie A9 virus and poliovirus type 1 were respectively recovered from cerebrospinal fluid and faeces. No increase of antibody titre against Coxsackie A9 virus could be demonstrated and a high titre of polio antibody was present. This case might also have been misleading if cerebrospinal fluid had not been examined.

Attempts were made to demonstrate a rise of antibody titre in paired sera, but the results were found to be irregular. A fourfold or more increase of antibody titre was demonstrated in 7 out of 19 cases. In nine cases, even with the recovery of Coxsackie A9 virus in cerebrospinal fluid, throat swab, or faeces, no significant increase of antibody was observed. Two further cases were interesting from a serological point of view. In Case 5 the patient showed a high antibody titre of 1 in 256 in the first serum and had a further rise to 1 in 4,096 in the second specimen. It may be recalled from the clinical description (see above) that this patient had a long biphasic illness, presumably due to relapse or recurrence. If the initial episode was the primary infection these sera were collected on days 33 and 52 after the onset, and it is not surprising that no virus was isolated. In Case 21 a rise in titre to 1 in 64 was obtained only in the third specimen of serum taken 70 days after the onset. It may be that in some enterovirus infections the antibody titre rises rather slowly. A similar pattern with a significant rise in titre only after two to three months was described by Barron *et al.* (1958) in two cases of E.C.H.O. type 2 virus infection. These irregularities may be attributable to the untimely collection of serum specimens in some cases; to the varied response of antibody production in human individuals, quite often to low titres only and sometimes with a late rise; or to the poor antigenicity of the viral agent.

Comparison of Two Outbreaks

In comparing the two outbreaks several points are of interest. Clinically the presence of rash, conjunctivitis, and oral lesions associated with Coxsackie A9 infection is in keeping with reports that these are more common in Coxsackie A than in Coxsackie B infections. The high incidence in children in 1961 (86% under 12) was that expected in Coxsackie infections and was much higher than in 1960 (only 24% under 12). Localized distribution and familial aggregation were also more pronounced in 1961 series, and in fact no cases of Coxsackie A9 infection among Service personnel occurred on Hong Kong Island. Several authors (Dalldorf, 1955; Stern, 1961) have commented that during epidemics of Coxsackie B infections paralytic poliomyelitis is relatively uncommon, while it may often occur in the presence of Coxsackie A infections. There was some evidence to support this in the two Hong Kong series, for, while paralytic poliomyelitis was relatively uncommon among Service personnel in 1960 (two cases), there were six cases, two of which were fatal, in 1961. The better recovery rate of virus in 1961 must be attributed to rapid transfer of specimens to a local laboratory with comparatively little delay in storage, in transit, and in actual performance of the tests.

Summary

Two summer outbreaks of aseptic meningitis among British Service personnel and their families in the Colony of Hong Kong in 1960 and 1961 are described and compared. In the first outbreak Coxsackie B1, B4, and B5 viruses and poliovirus 1 were isolated, while Coxsackie A9 virus was exclusively incriminated the following year. The main clinical difference was the presence of biophasic illness, rash, conjunctivitis, and oral lesions associated with infection by Coxsackie A9 virus but not the Coxsackie B viruses.

Localized distribution and familial aggregation were more pronounced with Coxsackie A9 infection and suggested an incubation time of 2 to 14 days. In some instances both poliovirus and a Coxsackie virus were isolated from the same patient. Antibody studies were valuable in determining the most likely aetiological agent in these cases. It appeared that paralytic poliomyelitis was more common in 1961, when Coxsackie A9 was causing aseptic meningitis, than in 1960, when Coxsackie B viruses were more prevalent.

We are grateful to Dr. D. J. M. MacKenzie, Honorary Director of Medical and Health Services in Hong Kong, for permission to publish; to Professor R. Kirk and Dr. R. E. Alvares for advice and encouragement; and to H. Shum, C. F. Chan, and Mrs. C. L. Ng for technical assistance. We would also like to thank Dr. Patricia Webb (U.S. Army Institute for Medical Research, Kuala Lumpur, Malaya) and Dr. A. D. Macrae (Virus Reference Laboratory, Colindale) for their help in some of the virology studies.

REFERENCES

Barron, A. L., Karzon, D. T., and Pollock, B. F. (1958). *Dis. Child.*, **95**, 235.
Chang, W. K., and Shum, H. (1962). *Amer. J. trop. Med. Hyg.*, **11**, 22.
Combined Scottish Study (1961). *Brit. med. J.*, **2**, 597.
Dalldorf, G. (1951). *J. exp. Med.*, **94**, 65.
—— (1955). *Ann. Rev. Microbiol.*, **9**, 277.
—— (1959). In *Viral and Rickettsial Infections of Man*, edited by T. M. Rivers and F. L. Horsfall. Lippincott, Philadelphia.
Girardi, A. J., Hummeler, K., and Olshin, I. (1957). *J. Lab. clin. Med.*, **50**, 526.
Grist, N. R., Larminie, H. E., MacGregor, L. G., McIntosh, E. G. S., McLaughlin, J., and Sommerville, R. G. (1960). *Scot. med. J.*, **5**, 355.
Hart, R. J. C. (1961). *Trans. Proc. roy. Soc. trop. Med.*, **55**, 301.
Lerner, A. M., Klein, J. O., and Finland, M. (1960a). *New Engl. J. Med.*, **263**, 1305.
—— —— Levin, H. S., and Finland, M. (1960b). Ibid., **263**, 1265.
Melnick, J. L. (1957a). In *Cellular Biology, Nucleic Acids and Viruses*, by V. G. Allfrey *et al.*, **5**, 365.
—— (1957b). *Ann. N.Y. Acad. Sci.*, **67**, 363.
—— Kaplan, A. S., Zabin, E., Contreras, G., and Larkum, N. W. (1951). *J. exp. Med.*, **94**, 471.
—— Ledinko, N., Kaplan, A. S., and Kraft, L. M. (1950). Ibid., **91**, 185.
Rhodes, A. H., and Beales, A. J. (1957). *Ann. N.Y. Acad. Sci.*, **67**, 212.
Stern, H. (1961). *Brit. med. J.*, **1**, 1061.
Syverton, J. T., McLean, D. M., Martins da Silva, M., Doany, H. B., Cooney, M., Kleinman, H., and Bauer, H. (1957). *J. Amer. med. Ass.*, **164**, 2015.

Details of the awards that are to be made for various aspects of rehabilitation during the ninth world congress of the International Society for Rehabilitation of the Disabled, which is to be held in Copenhagen in June, may be obtained from the Central Council for the Care of Cripples, 34 Eccleston Square, London S.W.1.