JAPANESE ENCEPHALITIS IN SINGAPORE CHILDREN*

By W. O. Phoon, M.B.,B.S., M.R.C.P., M.R.C.P.E., F.R.F.P.S., D.C.H.
and K. A. Lim, M.B., Ch.B., B.Sc., Dip. Bact.
(From the Departments of Paediatrics and Bacteriology, University of Singapore)
With the technical assistance of K. Kanapathipillai

1. INTRODUCTION

Japanese encephalitis exists in the endemic form on Singapore Island in common with many other parts of South-East Asia. Paterson et al (1952) and Hale (1952) first described the isolation of the Japanese encephalitis virus from human material in Malaya. Hale and Lee (1955) showed that about 70% of the population over the age of 12 years in Malaya, Singapore and Borneo possessed neutralising antibodies to the virus.

Most of the cases presenting with symptoms seem to be children. The present study was commenced in 1956, and is based on cases admitted into the Paediatric Unit of General Hospital, Singapore, during the years 1956-1962. The Unit admits children up to 10 years of age. As the Unit is the only children's medical unit on the Island apart from a small mission hospital, it can be assumed that most cases of encephalitis among children are admitted into it. Only cases with a clinical picture of encephalitis together with positive serological studies or isolations are included in this paper. A large number of other cases of encephalitis were encountered with negative or incomplete virological investigations. These have been excluded. The criteria for diagnosis by virological investigations are discussed below.

2. CLINICAL OBSERVATIONS

Geographical distribution. Most of the cases are found in the rural districts. This is probably due to the greater abundance of mosquitoes in those areas. There is also the possibility that a role may be played by animal reservoirs, such

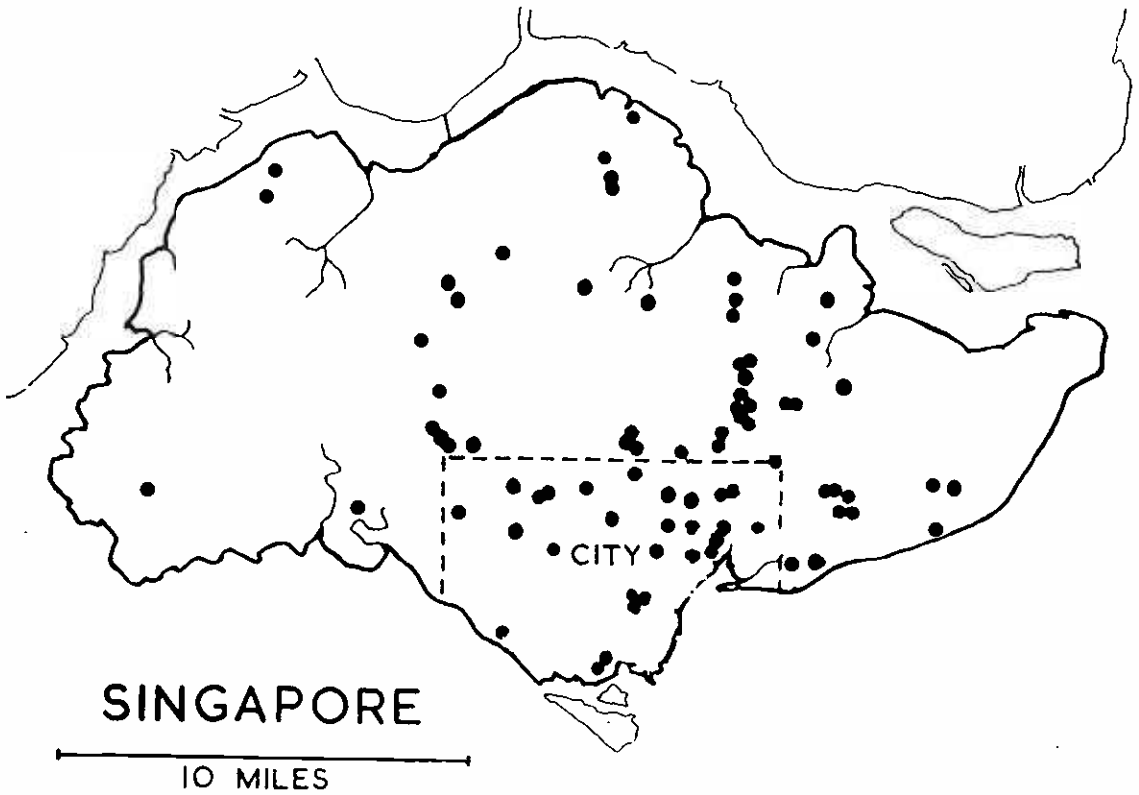

Fig. 1. Distribution of Japanese encephalitis cases in Singapore children, 1956-1962 study.

*Aided by a grant from the Rockefeller Foundation, New York.
Based on a paper presented at the W.H.O. Seminar on Japanese B encephalitis, Tokyo, 1962.

as pigs, which are also more abundant in rural areas (Fig. 1).

Age distribution. The majority were over 5 years of age. Only one was under 6 months of age (Table I).

Sex distribution. Males and females were almost equally affected.

Onset of illness. The illness usually started abruptly. Typically, a child came into hospital with a history of three days' illness, consisting of fever, malaise for three days, drowsiness and vomiting for about two days, and generalised convulsions on the day of admission. Usually, the convulsions were the reason for bringing the child to hospital.

Symptoms. The main symptoms and their frequency are listed in Table II.

From Table II it can be noted that fever occurred in all cases, with fits as the second commonest symptom. Slightly more than a third of the patients were admitted with a history of severe disturbance of consciousness. The majority of the others became drowsy or comatose during the next few days. A minority remained fully conscious throughout the course of illness. There was a complaint of headache in a quarter of the patients. The actual incidence is likely to be much higher, as many of the younger children were not articulate enough to tell of this symptom.

Physical Signs. The main physical findings on initial examination are listed in Table III.

Since the majority of the patients came into hospital soon after a fit, it was often difficult to know how much significance should be placed

TABLE I. AGE DISTRIBUTION.

Age group	No. of cases	Percentage of total
0 - 6 months	1	1.0
7-11 months	2	2.1
1 year	5	5.2
2 years	5	5.2
3 years	8	8.2
4 years	7	7.2
5 years	18	18.5
6 years	19	19.6
7 years	12	12.4
8 years	11	11.3
9 years	9	9.3
	97	100.0

TABLE II. SYMPTOMS.

Symptom	No. in which present	Percentage of total
Fever	97	100.0
Fits	57	58.8
Stupor or Coma	36	37.1
Vomiting	34	35.1
Headache	22	22.7
Cough	16	16.4
Diarrhoea	5	5.2
Giddiness	6	6.2
Constipation	4	4.1
Involuntary Movements	2	2.1
Anorexia	2	2.1
Incontinence	2	2.1
Limb stiffness	1	1.0
Muscle weakness	1	1.0
Neck pain	1	1.0
Difficulty in opening mouth	1	1.0

TABLE III. PHYSICAL SIGNS.

Physical signs	No. in which present	Percentage of total
Coma or stupor	65	66.9
Photophobia	2	2.4
Pupillary changes	8	8.2
Neck rigidity	50	51.5
Kernig's sign	17	17.5
Hypertonia	16	16.5
Hypotonia	10	10.5
Diminished deep tendon reflexes	13	13.4
Exaggerated deep tendon reflexes	4	4.1
Monoplegia	2	2.1
Hemiplegia	6	6.2
Facial palsy	4	4.1
Extensor plantar response		
Unilateral	13	13.4
Bilateral	17	17.5

upon physical signs present on admission such as coma, stupor, meningism, changes in tendon reflexes and motor weakness, as they can all occur as postictal phenomena.

In addition to neck rigidity and Kernig's sign, a number of cases had stiffness of the back. The pupillary abnormalities included dilatation, constriction and sluggish reactiveness, doubtless depending on the degree of coma present. Abnormalities of the extraocular muscles such as strabismus were noted sometimes as transient phenomena. The fundi were normal in most cases. In a few cases there were widespread haemorrhages in the retinae. No papilloedema was observed.

In addition to the signs listed above, a notable feature at the onset of the disease is the presence of a very high fever, often exceeding 105°F. This is fairly characteristic.

3. COURSE OF THE DISEASE

The unpredictable variability of physical signs from day to day is very striking. In the typical case, the child remains comatose or stuporous for about eight to nine days after the onset of illness. Loss of tendon reflexes, often isolated and unilateral, occurs quite commonly and transiently. Muscle tone and tendon reflexes may vary considerably from day to day. The abnormal signs may shift from side to side or from limb to limb. Indeed, they can be described as "fleeting and flitting" in character, not unlike the joint pains of rheumatic fever.

About the sixth or seventh day of illness, the temperature starts to fall by lysis, and often returns to normal by the eighth or ninth day. About this time the child regains complete consciousness, often dramatically. On one day, he can be moribund or stuporous; plucking at his bedclothes; toying with his genitalia; performing bizarre, groping, purposeless movements; grimacing and shrieking when disturbed; and tossing about with half-closed eyes. The next day he can be found sitting up in bed, quite placid, alert and cooperative — almost a different person altogether.

Almost every patient exhibited a disturbed state of consciousness, ranging from apathy or irritability to deep coma. The disturbances can be very bizarre. Quite a few have hallucinations after apparent recovery. Many become emotionally unbalanced. The older children may revert to the infantile stage, and become incontinent and indulge in thumb sucking. Temper tantrums are not uncommon. The average duration of coma or stupor was about a week. Some cases remained in deep coma for one to two months and yet made a recovery, although this is incomplete in such cases.

Fatal cases. There are only seven deaths in this series. One other child died about six months after an apparently complete recovery. It was not possible to ascertain the exact cause of death. Of the seven cases who died in the acute stage, two were four years, two were five years, one was six years, and two were seven years of age respectively. All presented with fever, five with drowsiness, four with fits and three with vomiting. Five were comatose or stuporous on admission, but all rapidly lapsed into

coma subsequently. Two died on the third day, three on the fourth day, one on the fifth day and one on the seventh day of illness. No special features were observed apart from the fulminating course of the illness. In all these cases a virus was isolated from the brain and identified as the Japanese encephalitis virus.

4 CEREBROSPINAL FLUID

Several of the initial lumbar punctures yielded a normal fluid on microscopical and biochemical examination. All the cases, however, except one had abnormal cerebrospinal fluids on a repeat puncture. The cell count was usually in the region of 30-150 (maximum in the series, 400) per c.mm. The cells were polymorphs in the first few days of illness, being replaced by lymphocytes later on. The protein content was slightly raised, but below 100 mgm.%. In only one case was a specimen obtained with a protein of more than 100 mgm.% (110 mgm.% in that instance). The other specimens from the same patient all had a protein content of below 100 mgm.%. The glucose level was never low — always above 40 mgm.% and usually above 50 mgm.%.

5. HAEMATOLOGICAL STUDIES

In the first week of illness there was often a polymorphonuclear leucocytosis of 15,000 to 20,000 per c.mm. There was no observed change in the other elements of the blood.

6. VIROLOGICAL STUDIES

The cases in this series were those in which infection by Japanese encephalitis virus (JEV) was confirmed by serological tests or virus isolation. Cases in which laboratory tests were negative or not conclusive, or in which clinical data were inadequate, were excluded. With the exception of a few cases where only one specimen was available, at least two serum specimens from each case were examined for antibodies for Japanese encephalitis virus (Nakayama strain) antigens. The first specimen was obtained usually within one to two weeks of the onset of the disease and the second specimen usually two weeks later.

Complement fixation tests (CFT) were performed by the drop method in moulded plastic trays. Antigens were prepared by the saline extraction of infected mouse brain with five cycles of freezing and thawing. Guinea-pig complement was used at 2 units and sheep cells sensitised with 8 to 16 units of haemolysin. One drop was approximately 0.02 ml.

Neutralisation tests were performed in adult mice inoculated intracerebrally with mixtures of serum, (inactivated at 56°C for 1 hr.) and virus dilutions. A serum was considered positive if it protected more than 3 out of 6 mice inoculated with 100 LD_{50} virus.

90 cases were tested by CFT and 72 of these by NT against JEV antigens. A case was considered confirmed serologically if there was at least four fold-rise of CF antibody (71 cases) or if the CF titre exceeded 1/32 (19 cases). Neutralising antibody was frequently present in the first specimen (45 cases), when the second specimen was not tested. Where the first specimen was negative, the second specimen was always positive (27 cases). Since the NT results always confirmed the CF results, it was abandoned towards the end of the study.

In view of the possibility that JEV antibodies detected might have arisen from some other Group B arbovirus infection, dengue type-1 antigen was used in CFT against sera of the last 24 patients in the series. All these patients had no antibody for dengue type-1 antigen, although such antibodies had been detected previously in sporadic dengue cases. Since 1960, however, dengue viruses have been circulating freely in Singapore and a number of encephalitis cases have occurred recently where the patients' sera show rise of CF titre to equal levels for both JEV and dengue antigens. (Many cases of dengue virus infection have rise of antibody for JEV antigens). Whenever CF and NT results show antibodies for both JEV and dengue antigens, it is good policy not to draw any conclusions from the tests.

Virus was isolated by intracerebral inoculation of infant mice from brains obtained at autopsy on seven patients who died. These virus isolates were identified as Japanese encephalitis virus types by neutralisation tests in adult mice against immune serum to the Nakayama strain. In each instance, the virus isolate was neutralised to nearly homologous titre. Many attempts were made to isolate virus from the first serum specimen by intracerebral and intraperitoneal inoculation of infant mice, by inoculation in 6 day old chick embryos, all without success. 30 specimens of C.S.F. tested were also negative.

A number of patients who died before antibodies could be demonstrated in their sera were excluded from the study because brain isolation was negative or permission for autopsy was refused. Again, virus isolations from autopsies on patients who had not been studied adequately before death were also excluded from this study.

7. SEQUELAE

We find it is rather difficult to give an accurate assessment of the incidence of sequelae. Often the sequelae are undetectable till after a period of some years, especially in infants and very young children. This applies more to behaviour disorders and mental subnormality than to physical disabilities which are usually more apparent.

Of the 90 children surviving the acute stage of the disease, 82 were followed up for periods of time varying from a few months to six years. The results are listed in Table IV. Transient paralyses and behaviour disorders in the acute stage of the disease are not included as sequelae. The initial assessment of sequelae was done one to two months after the onset of illness, when the child had been discharged from hospital for some length of time.

39 children had no obvious sequelae of any kind (47.9%). 43 children (52.1%) had either physical or mental sequelae or behaviour disorders or a combination of two or three of these.

The figures given in Table IV have to be interpreted in the knowledge that there can be quite considerable changes in the nature and severity of the sequelae after the acute stage of the disease. The motor defects tend to improve for a year or so. Mental backwardness and behaviour disorders, on the contrary, may not be apparent for some months or even longer. For the preschool child, assessment of mental faculties can be a very difficult task. For the child who has already started to go to school, a temporary falling back in scholastic standards and examination results is only to be expected after a severe illness and a prolonged stay in hospital with all its attendant psychological trauma. Hence only a long-term follow-up can give a realistic picture of the extent of damage caused by the disease.

Eight children were followed up for more than one year but less than three years. One was mentally backward. One developed an emotional disorder.

Six children were followed up for more than three years but less than four years. One was mentally backward. One had motor paralysis.

Eight children were followed up for four years or longer. Two had both paralysis and mental backwardness. One was mentally backward and had behaviour disorders. One was slightly mentally backward and doing poorly at school.

With regard to mental backwardness, it must be emphasized that we had to rely heavily on the parents for accounts of the mental state of the child before the illness. In the case of schoolchildren, we also used school reports and consulted the teachers for means of comparison with the subsequent mental state. Many parents of affected children volunteered information to the effect that the child had become very absent-minded and forgetful, that he forgot the whereabouts of an object almost as soon as he had kept it. Some teachers complained that the child was mislaying pencils and books almost daily. In some instances, a child who was consistently at or near the top of his class never recovered sufficiently to pass examinations or to do better than the bottom one-fifth of the class. One boy, aged 14 years, has been followed up for more than five years. He had topped the class on several occasions before his illness five years ago. Since then he has done very poorly. For the past two years he has not been promoted to a higher form.

Behaviour disorders can take various forms. Some children become very apathetic. More become aggressive, bellicose and violent. The younger children can be very hyperkinetic and difficult to manage. Some develop temper tantrums on slight provocation. Some postencephalitics become very hyper active, as described by Russell (1942).

TABLE IV. SEQUELAE.

Sequelae	No. of cases	Percentage of total
Motor weakness		
Hemiplegia	21	25.9
Monoplegia	2	2.5
Diplegia	1	1.2
Facial palsy	1	1.2
Fits	2	2.4
Mental backwardness	8	9.8
Behaviour disorder	8	9.8

8. PROBLEMS OF DIAGNOSIS

One of the chief difficulties of diagnosis in Singapore is due to the fact that Japanese encephalitis is present the whole year round. There are no epidemics to sharpen the clinician's index of suspicion.

In the typical case, the history of fever, drowsiness, vomiting and fits strongly suggests an acute inflammatory disease of cerebral origin. Here the main differentiation is from septic meningitis, but can quite easily be excluded by examination of the cerebrospinal fluid. A difficulty may arise when cases of septic meningitis are admitted after having been partially treated with broad-spectrum antibiotics without a record of physical signs observed before such treatment had been instituted. Such cases may have a relatively clear cerebrospinal fluid with a mild pleocytosis and a slightly elevated protein only. However, the glucose content in most instances is still low, unlike in encephalitis.

Aseptic meningitis due to viruses cannot be distinguished with certainty from encephalitis on clinical or cerebrospinal fluid examination. It tends to cause less disturbances of consciousness and more signs of meningeal irritation, but the differences are only relative.

Tuberculous meningitis has usually a more insidious onset. In the cerebrospinal fluid, the main difference is in the glucose content, which is low in tuberculous meningitis, in contrast to the normal content in encephalitis. The protein content in tuberculosis is often considerably elevated above 100 mgm.%. This almost never occurs in encephalitis.

When poliomyelitis affects mainly the brain, clinical differentiation from Japanese encephalitis can be difficult. Usually, however, the disease affects the medulla or spinal cord as well, giving rise to signs of lower motor neurone disease. Some cases of Japanese encephalitis do show signs of lower motor neurone involvement in the form of absent or diminished tendon reflexes, but these are usually transient.

Haemorrhagic fever (due to strains of dengue virus) can simulate encephalitis in producing drowsiness, considerable disturbances of the sensorium and fits. At the time of writing of this paper, there is an epidemic of haemorrhagic fever, mainly among children, in Singapore. There are, however, typically haemorrhages into skin or internal organs due to thrombocytopenia, a major characteristic of the disease. There is a leucopenia in the acute stage, unlike in Japanese encephalitis where there is usually a leucocytosis. The cases to date presenting with gross disturbances of consciousness under study by the authors have no changes in the cerebrospinal fluid, even on repeated examination.

In brain abscess there is often a focus of septic infection such as otitis media. The cerebrospinal fluid may show slight abnormalities. The diagnosis has to be considered especially in the presence of persistent focal signs of cerebral involvement.

It does not appear to be possible to differentiate encephalitis due to other viral agents on clinical grounds alone.

Upper respiratory and other infections can be accompanied by vomiting, drowsiness or fits. The drowsiness can be produced or aggrevated by the administration of sedatives or opium derivatives (which occurs not uncommonly in Singapore). Diagnosis is made by lumbar puncture, as the cerebrospinal fluid in such cases is normal.

Cryptococcal and other fungal meningitides have usually a low glucose content in the cerebrospinal fluid.

9. MANAGEMENT

As far as the authors know, there is no specific drug of proven value for this disease. Nevertheless, careful management of the child is important as regards treatment of hyperpyrexia, prevention of superadded infection, care of bladder and bowels, and prevention and care of bedsores.

In the acute stage of the disease, hyperpyrexia is a frequent and formidable problem. In our experience, the standard measures for reducing high fever — tepid sponging, ice-packs, exposure and antipyretic drugs — are relatively ineffective. Newer drugs such as chlorpromazine and acetoamino-phenol have not been found very useful.

For frequent fits, the judicious use of paraldehyde or phenobarbitone is recommended. A broad-spectrum antibiotic is used routinely to prevent superadded infection. Corticosteroids have been tried in some cases with uncertain results.

Sequelae and complications are treated as they arise. Physiotherapy and orthopaedic measures for muscular weakness or deformity; antiepileptic drugs for fits; tranquillizers and psychotherapy for behaviour disorders; and placement in institutions for the severe mental defectives are some of the lines of management resorted to.

10. DISCUSSION

The symptoms, signs and laboratory results in the cases of this series are not significantly different from those reported in previous series, e.g. Lewis et al (1947) and Dowling and Webb (1959). The endemic nature of the disease in this country sometimes presents problems of diagnosis. For the purposes of this paper, we have included only those cases which fulfilled the accepted criteria of serological diagnosis or from which a virus has been isolated. There are in addition several other cases being studied with negative serological investigations but which presented as encephalitis clinically with compatible cerebrospinal fluid findings. These could be either cases of Japanese encephalitis which for some reason did not develop a significant rise of antibody titre, or cases of encephalitis due to other infective agents. In our study, the sample of convalescent serum was usually taken two weeks after the first. Findings of some cases suggest that there may be a delay in the rise of antibody titre. A third specimen of serum two weeks after the second would seem indicated in doubtful cases.

The mortality of 7.2% (7 cases) seems low compared with that of many other series, e.g. Chuetal (1940), Sabin (1947) and Sabin et al (1958). The Paediatric Unit of General Hospital, Singapore, takes in almost every case of a child less than 10 years old with a non-surgical illness severe enough to warrant hospitalization. Hence it is quite unlikely that there was an appreciable number of fatal cases of Japanese encephalitis not included in the series. It is possible that some cases had such a fulminating course that they died without the diagnosis having been made. We have also excluded a few suspected cases in which virus isolation was negative or permission for autopsy refused. As it stands, the low mortality might have been due to a level of partial immunity in the affected children, or to a relatively low virulence of the strain of virus in Singapore.

The incidence of sequelae, on the other hand, appears high compared to that noted by several other workers, Wako et al (1952) and Bajpai et al (1958). It may be pointed out that there are rather few large series of long-term follow-up studies of Japanese encephalitis among children. As was discussed above, some sequelae required some time before manifesting themselves, as pointed out by Heersema (1940).

There is a negligible incidence of complications. This can be attributed at least partly to the use of broad-spectrum antibiotics routinely, with a consequent reduction of superadded infections.

ACKNOWLEDGMENTS

We thank Professor J. H. Hale, formerly head of the Department of Bacteriology, University of Malaya, who initiated much of the virological aspect of this study; Dr. Gwen D. Smith, for her advice and encouragement; Professor C. E. Field, Professor H. B. Wong, and Dr. Q. G. Quah for permission to examine patients under their care; and to the staff, past and present, of the Paediatric Unit of General Hospital, Singapore, for their constant and helpful cooperation.

REFERENCES

Bajpai, P. C., Dikshit, S. K., Sharma, J. C. and Gupta, N. P. (1960): Acute epidemic encephalitis in children (Lucknow, 1958): a clinical study. J. Indian Med. Ass. *35*, 1.

Chu, F. T., Wu, J. P. and Teng, C. H. (1940): Acute encephalitis in children. Chinese M. J. *58*, 68.

Dowling, M. A., and Webb, H. E. (1959): A preliminary report on encephalitic type of illnesses in Singapore. J. R. Army M. Corps. *105* (i), 28.

Hale, J. H., Lim, K. A. and Chee, P. H. (1952): Japanese type B encephalitis in Malaya. Ann. Trop. Med. & Parasit. *46*;220.

Hale, J. H. and Lee, L. H. (1955): Serological evidence of the incidence of Japanese B Encephalitis Virus infection. Ann. Trop. Med. & Parasit. *49*, 293.

Heersema, P. H. (1940): Prognosis in postencephalitic behaviour disorders. M. Clin. North America, *24*, 1179.

Lewis, L., Taylor, H. G., Sorem, M. B., Norcross, J. W. and Kindsvatter, V. H. (1947): Japanese B encephalitis: clinical observations in outbreak on Okinawa Shima. Arch. Neurol. & Psychiat. *57*;430.

Paterson, P. Y., Ley, H. L., Wisseman, C. L., Pond, W. L., Smadel, J. E., Diercks, F. H., Hetherington, H. D. G., Sneath, P. H. A., Witherington, D. H., and Lancaster, W. E. (1952): insolation of virus and serological evidence of human and equine infections. Am. J. Hyg. *56*;320.

Russell, J. A. (1942): Hyperactive child. Am. J. Dis. Child. *63*, 94.

Sabin, A. B. (1947): Epidemic encephalitis in military personnel. J.A.M.A. *133*, 281.

Sabin, A. B., Schlesinger, R. W., Ginder, D. R., Matumoto, Minoru. (1947): Japanese B encephalitis in American soldiers in Korea. Am. J. Hyg. *46*;356.

Wako, H. et al (1952): Clinical picture of Japanese B encephalitis in children in 1948. Tohoku J. Exper. Med. *55*, 177.