A combination of histological examination of the central nervous system and attempted virus isolation from the blood has been shown to detect a greater number of infections by the Brunenders strain than either method used separately. Viraemia is the rule rather than the exception in infected cynomolgus monkeys, whereas virus has been isolated from the blood of rhesus monkeys only when the larger cortisone doses have been used, and in these animals the viraemia has been of shorter duration than with cynomolgus monkeys.

The cortisone schedule is different from that employed in America, divided doses being used and continued until the 22nd day of the observation period. This seems to prolong viraemia in cynomolgus monkeys and so makes virus isolation from the blood more probable.

Some doubts have been expressed on whether the monkey safety test is necessary in addition to the tissue-culture test. The American experience, however, would indicate that the monkey test is an essential part of the safety-testing procedures, since it was in monkeys conditioned with cortisone, or cortisone combined with x-radiation (Eklund *et al.*, 1956; Syverton *et al.*, 1956), that virus was isolated from vaccine suspected of causing infection, whereas in unconditioned monkeys and in tissue culture isolations were made only with difficulty.

Slight modifications of the American method have been made in the tissue-culture safety test. Ten ml. of vaccine is inoculated initially on to each bottle cell culture without further dilution, the freshly dialysed vaccine itself acting as the nutrient medium. We have found no evidence that undiluted vaccine inhibits virus infectivity. Youngner (1956) has shown that the absorption of polio virus on to cells is related to the volume of fluid in which the virus is suspended, and we have found that the number of virus particles that can be detected in a given volume of fluid is decreased by increasing the depth of medium over the cell cultures. Three to four days are allowed for absorption of virus into cells before a further 10 ml. of 199 solution is added in order to ensure good cell maintenance until the replacement of medium after the first week's incubation. Initial cell cultures are always kept for 21 days after inoculation with vaccine and the weekly subcultures for 14 days, whereas in America only 14 and 7 days respectively are required for these procedures. It has been found in titrations of virus suspensions that the type III virus may take more than two weeks to produce a cytopathic change in monkey-kidney cultures. This has not yet been noted with either the Brunenders or MEF-1 strains, these viruses having produced a cytopathic change within 14 days.

So far "foamy agent" (Rustigian *et al.*, 1955) has been the only real problem with the cell cultures. This agent has been more prevalent in the early months of 1956 and 1957 than during the summer and autumn of 1956. As it does not manifest itself until the third week of incubation of cell cultures, 2,500 ml. of vaccine has been inoculated initially during these months in order to ensure that at least 1,500 ml. is tested on good cells without the loss of time involved in repeating the tests. Other wild viruses have not given any trouble. In only one instance has a simian virus other than "foamy agent" been encountered. Monkeys used for tissue culture are housed two to a cage from the time of arrival and are not used until they have been in the laboratory for at least seven days, and are usually kept much longer. This treatment may reduce the continuous sub-clinical passage of viral agents that must take place when many animals are housed together in large cages, as is the practice in most laboratories dealing with large numbers of monkeys.

The test for antigenic potency in rhesus monkeys is similar to that used in the United States except that the British Standard Sera are employed as controls instead of those issued by the National Institutes of Health. The antigenic activity of some of the batches of vaccine have also been studied in children, and the antibody responses obtained have shown good agreement with those obtained in monkeys (M.R.C., 1957). An investigation of the value

of guinea-pigs and cotton-rats as an alternative to monkeys is also being made.

Fuller accounts of our observations on the behaviour of the Brunenders strain in monkeys, on the histopathological aspects of vaccine control, and on the antigenicity tests will be published later.

Summary

The safety and potency tests carried out by the Biological Standards Control Laboratory on formalized trivalent poliomyelitis vaccine are similar to those in use in the United States, but the introduction of the attenuated Brunenders strain into the British vaccine in place of the more virulent Mahoney strain has necessitated some modifications of the American practice.

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"POLIOENCEPHALITIS": A CLINICAL AND LABORATORY STUDY

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For many years it has been believed that poliomyelitis might be manifested by an encephalitis either with or without the usual signs of paralytic poliomyelitis. In nearly all the earlier reports there was only epidemiological or clinical evidence to show that the cases were due to the same agent as paralytic poliomyelitis. Altogether five cases of encephalitis have been reported in which isolation of the virus of poliomyelitis was made (Kelleher *et al.*, 1949; Jennings *et al.*, 1949; Barrett *et al.*, 1952; Adler *et al.*, 1955). The clinical manifestations of encephalitis included somnolence or coma, tremors and incoordination, nystagmus, loss of conjugate eye movements, muscle rigidity, and hemiparesis.

An epidemic of poliomyelitis occurred in 1955, and 121 cases of paralytic poliomyelitis were admitted to this hospital. During the epidemic period nine cases initially classified as encephalitis were seen (eight at Lodge Moor Hospital), and these were studied by clinical and laboratory means. In seven of the nine there was definite evidence of simultaneous infection by polio virus. The eighth case was thought to be disseminated sclerosis, and the last had polyarteritis nodosa with brain involvement.

Laboratory Methods

The laboratory methods were based on those used in Melnick's laboratory (Kraft and Melnick, 1950; Black and Melnick, 1954; Melnick, 1955). Virus isolation was attempted by inoculating suspensions of faeces into monkey-kidney-tissue cultures. Complement fixation was carried out on paired sera against all three types of polio virus with serum dilutions from 1/4 upwards (Balducci *et al.*, 1956). In Cases 1-5 and 8 complement-fixation tests were done against herpes simplex, adenoviruses, and Coxsackie virus types A1-A8, A10, B1, B3, and B4. The results were negative except where indicated in the Table.

The frequency of positive results for polio virus and the type of serological response obtained were very similar to those obtained in a control series of cases of typical paralytic poliomyelitis (Tyrrell *et al.*, 1957). Polio virus infection was indicated when virus was isolated from the faeces or when a rise in neutralizing antibody titre occurred. In some cases the diagnosis was supported by the presence of complement-fixing antibodies.

Results

The laboratory tests as presented in the Table indicate that Cases 1-7 were associated with polio virus infection. This evidence was based on virus isolation in five, and on a rise in antibody titre in two.

In Cases 1-3 there was no disturbance of consciousness, but after a brief feverish illness with some upper respiratory symptoms and headache the patient was admitted with meningism, nystagmus, and signs of a slight upper or lower motor neurone paralysis. In Cases 4-7 there was a similar but more severe illness, with marked disturbances of consciousness and in Case 7 a fatal result.

The C.S.F. was abnormal in all these cases, the protein ranging from 30 to 85 mg. per 100 ml., and the cell count from normal to 50 per c.mm. Protein and/or cells were raised and the cells were either mainly or entirely lymphocytes.

In Case 6 an E.E.G. was done which showed an abnormal tracing (see Fig.). On regaining consciousness this child showed pica and attacked other patients, but finally made a complete recovery. The cases were followed up for from two to eight months, and residual signs seen included conjugate deviation of the eyes (Case 7), facial paralysis (Case 5), persistent nystagmus (Cases 2, 3, and 4), and wasting of

pectoral muscles (Case 3). The ataxia, hypertonia, and increased reflexes disappeared in one to two months.

Case 8 was thought clinically to be a case of disseminated sclerosis with an acute onset. Specimens were not collected till six weeks after admission and showed evidence

Electroencephalogram recorded from Case 6. Patient stuporous six days after onset. Frequent bouts of generalized high amplitude, 2-3 c/s waves occurring simultaneously in all areas.

of a recent polio virus infection which may have been acquired in hospital. Case 9 was found at necropsy to have periarthritis nodosa with gross lesions in the pons, as well as in the kidney, liver, and lungs. Cases 8 and 9 show no evidence of concurrent polio virus infection.

Discussion

Our first three cases resemble the syndrome of acute cerebellar ataxia, which in a few other cases has been shown to be associated with polio virus infection (Berglund *et al.*, 1955; Huston *et al.*, 1956). The loss of consciousness in Cases 4 to 7 may be due to lesions in the brain stem, which may also account for the involvement of the pyramidal tract (Bodian, 1952). There was no clinical evidence of respiratory embarrassment to account for the loss of consciousness in these cases (Minnesota Poliomyelitis Research Commission, 1947). The fact that seven of these cases showed evidence of polio virus infection is not proof that the illnesses were caused by that virus. However, the laboratory results obtained were similar to those found in typical paralytic poliomyelitis. The clinical manifestations were very like those found in the five other cases mentioned in the literature.

We do not know whether cases of this clinical type are always associated with polio virus infection. It would be

Summary of Clinical and Laboratory Findings in 9 Cases of "Encephalitis"

Case	Special Clinical Features	Results of Tests for Polio Virus						Virus Isolation Faeces
		Complement Fixation			Neutralization			
		I	II	III	I	II	III	
1	{ Unilateral hypertonia and Babinski, ataxia, nystagmus, gaze-paresis	16*	16	10†	> 512	> 512	512	Type I
		10*	10	16	> 512	> 512	512	
2	{ Coarse horizontal and vertical nystagmus, diplopia	4	4	8	64	32	> 512	"
		8	4	16	64	32	> 512	
3	{ Gross ataxia, pareses, normal reflexes, wasted pectorals, persistent nystagmus	< 4	16	16	> 512	64	> 512	Neg.
		4	8	8	> 512	> 512	> 512	
4	{ Semicoma, hypertonia, gaze-paresis, ataxia, persistent nystagmus	< 4	< 4	4	> 512	32	> 512	Type I
		< 4	< 4	< 4	256	32	> 512	
5	{ Coma (4 days), hypertonia, facial paralysis, squint, anisocoria, ataxia	< 4	< 4	< 4	128	256	—	Neg.
		< 4	< 4	< 4	1,024	> 512	32	
6	{ Stupor (5 days), hyperkinesia, areflexia, bilateral Babinski, bizarre behaviour, complete recovery	12	10	12	1,024	—	> 2,048	Type I
		32	20	32	1,024	—	> 2,048	
7	{ Coma, muscular twitching, conjugate deviation, nystagmus, tachypnoea, death	—	—	—	—	—	—	"
8	{ Girdle pains, urinary retention, clonus, myoclonic twitching, nystagmus, impaired vibration sense	4	16	16	< 32	> 512	> 512	Neg.
		< 4	8	4	< 32	> 512	> 512	
9	{ "Fit"—stupor, photophobia, hyperkinesia, coma, periodic breathing, death	< 4	< 4	< 4	> 8	> 8	> 8	"

* In each case the upper row of figures are titres obtained with acute phase serum, and the lower row are titres obtained with convalescent serum.

† Also showed rising titres against Coxsackie A 1, A 4, A 6

necessary to study cases occurring in other seasons and at other places in order to settle this point.

Summary

During the 1955 poliomyelitis epidemic 121 cases of clinically typical poliomyelitis were admitted to hospital. In the same period nine cases of encephalitis-like illness were seen. These were investigated by standard virological techniques, and seven were shown to be infected with poliomyelitis virus. The infected cases fell into two groups—those which resembled acute cerebellar ataxia, and those which resembled acute encephalitis. Probably poliomyelitis infection can occasionally manifest itself by symptoms exclusively related to cerebellar or "encephalitic" lesions.

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HABITUAL ABORTION DUE TO INSUFFICIENCY OF THE INTERNAL CERVICAL OS

A PRELIMINARY REPORT OF SEVEN CASES TREATED BY A MODIFIED SHIRODKAR TECHNIQUE

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The problem of habitual abortion is fortunately relatively rare. To the woman who suffers from this condition, however, it is a most serious and depressing one. Despite every line of investigation and management, there is still a hard core of patients who habitually abort in the early months of pregnancy.

Aschoff (1906) demonstrated the intimate anatomy of the uterus and cervix, showing that the upper part of the cervical canal and the anatomical internal os were incorporated into the lower segment of the uterus at an early stage of pregnancy (Fig. 1). This was confirmed by F. J. Browne (1950). Danforth (1947), of Chicago, showed that as a result of congenital defect or of trauma by dilators, forceps extraction, or the passage of a large infant, the fibromuscular junction between the anatomi-

cal internal os and the lower uterine segment might be rendered inefficient for its purpose of retaining the growing conceptus *in utero* (Fig. 2). Clinically such a condition may be suspected in patients who, following

FIG. 1.—Showing formation of the lower uterine segment by inclusion of the upper part of the cervical canal in the uterine cavity.

surgical dilatation or amputation of the cervix, or trauma during delivery, subsequently abort repeatedly at a stage in pregnancy which will vary according to the degree of cervical impairment present.

Lash and Lash (1950) drew attention to the incompetent internal os as a factor in habitual abortion, but particularly in relation to anterior defects resulting from obstetrical or gynaecological trauma. They described a method of repair of the anterior defect. Subsequently Rubovits, Cooperman, and Lash (1953) described a means of diagnosis in the non-pregnant state by means of x-ray examination. The symptoms are, of course, present only during pregnancy, and consist of a sudden rupture of the membranes followed by a rapid and relatively painless extrusion of the products of conception. It seems curious, however, that Lash and Lash should describe only an anterior defect, for most gynaecologists would agree that lateral defects in the cervix are far more common. Shirodkar (1955), however, realizing that the defect in the internal os could be, and

FIG. 2.—To show how bag of membranes may descend or herniate if fibromuscular junction is weak or insufficient, with rupture of membranes and/or abortion.

realizing that the defect in the internal os could be, and