*For Debate . . .***A Neurological Note on Vaccination against Influenza**

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Vaccination against influenza may be complicated by a neurological illness. Two case histories are presented together with a summary of seven others.

Introduction

Though annual vaccination against influenza is an important safeguard for patients with chronic chest disease and incipient cor pulmonale,¹ the epidemiology of influenza is so unpredictable² that arguments in favour of mass vaccination are less convincing. As the neurological complications which sometimes follow influenza³ might be quoted among the many unimportant reasons for being vaccinated, practitioners should know that the procedure has its own neurological risks.

Despite the lapse of time since the first field trial,⁴ vaccines which are both reliable and free from side effects have been slow to appear. Oil adjuvant preparations are an advance on the earlier saline vaccines but may cause unpleasant or dangerous reactions. These include fever, skin nodules and abscesses, and hypersensitivity to egg protein used in manufacture.

Neurological disorders, like those which follow other forms of prophylactic inoculation⁵ might be expected to occur but none were mentioned in three recent reviews published in this country.⁶⁻⁸ Occasional cases, however, have been reported in the United States of severe central nervous reaction, beginning hours or days after vaccination. Two patients lapsed into coma—one after eight hours⁹ the other after eight days¹⁰—two developed encephalitis,¹¹ and another meningoencephalitis.¹² All five recovered. The diagnosis of postvaccinal neurological illness is presumptive; there is at present no way of proving or disproving the aetiological relationship. An abnormal immune response is thought to be the mechanism.

The case histories of two examples of the disorder are given below. The first (Case 1) had acute transverse myelopathy which began on the 29th day after vaccination. His recovery was complete and he has remained well over the next eight years. The second (Case 8) developed occlusion of a central retinal vein some 16 or more days after revaccination. Symptoms subsided after several months with return of vision and of the fundoscopic appearance to normal.

An episode of disseminated sclerosis is always a major differential diagnosis of transverse myelopathy. The issue can be decided only by the preceding history and follow-up:

in this case there had been no previous episode and, after eight years, no relapse. There is, however, no limit to the interval between attacks of demyelination, some of which may be precipitated by prophylactic procedures.

Occlusion of the central retinal vein has been reported after Jennerian vaccination¹³ together with other disorders of the retina and optic nerve. In the present example the early postvaccinal symptoms followed by a period of well-being before the occlusion occurred are typical of an illness due to abnormal immune response.

Through the kindness of Dr. K. W. Lovel it has been possible to trace six other cases which had been reported to the Committee on Safety of Drugs. The clinicians concerned have very generously consented to publication of the essential details (Cases 2 to 7 in Table). Dr. G. Homann, Chief of the West German Commission on Drugs, has kindly sent an account of a case reported to him (Case 9).

Case 1

On 9 October 1963 an industrial chemist aged 23 was vaccinated against influenza. The vaccine* was a saline suspension of equal parts of inactivated A and B viruses, emulsified in mineral oil. Twenty-nine days later, on 7 November, he was troubled by irritation over the front of his chest which spread round to his back, on to his abdomen, and finally down both legs to his feet. After 48 hours he developed backache, ataxia, dysuria, and constipation. When examined in his lodgings on 12 November, he had a flaccid paraparesis with absent knee and ankle jerks, absent abdominal reflexes, and bilateral extensor plantar responses. There was a sensory level at D 4 to touch, pain, temperature, and vibration sense immediately above a narrow band of hyperaesthesia. Cranial nerves and upper limbs were normal, the arm jerks were brisk.

He was admitted to his local hospital. The spinal fluid was clear, with normal manometry. It contained 30 W.B.C. per mm³ and 40 mg of protein per 100 ml. Other investigations were normal, including culture of faeces and of spinal fluid for virus.

The results of virus complement fixation tests were as follows: 14 November—influenza A 1/32, influenza B 1/16, influenza C 1/32, and mumps V 1/64; 21 November—influenza A 1/64, influenza B 1/16, influenza C <1/8, and mumps V 1/32. Titres to parainfluenza 1, 2, and 3, adenovirus, Q fever, psittacosis-lymphogranuloma venereum, lymphocytic choriomeningitis, mumps S, streptococcal MG agglutinins, cold agglutinins, and the Paul-Bunnell reaction were all <1/8 in both samples. The titres to influenza A and B were unusually low, as the average titres at four weeks after vaccination were found to be 1/192-1/384 for A virus and 1/96-1/192 for B virus, levels below 1/48 and 1/32 respectively being exceptional (C. H. Smith, personal communication, 1964). Serum was not available for haemagglutination-inhibition tests at a later date.

Complications of Influenzal Vaccination

Case No.	Sex	Age	Date of Illness	Onset after Vaccination	Diagnosis	
2	M.	58	Dec. 1963	2 weeks	Polyneuropathy	Sore throat at time of vaccination. C.S.F.: 180 mg protein/100 ml. Slowly improved
3	M.	15	Dec. 1963	4 days	Encephalopathy (bulbar paralysis)	Died in coma on 17th day. Known diabetic. C.S.F.: lymphocytosis. No virus isolated, but fluid injected into suckling mice caused paralysis on 3rd day
4	F.	55	Oct. 1964	7 days	Transverse myelopathy	C.S.F.: normal at 6 and 10 weeks after onset. Slowly improved
5	M.	11	Sep. 1965	1 day	Encephalopathy	C.S.F.: 50 W.B.C./mm ³ (75% lymphocytes). Measles: 1/160 in each of two serial samples. Unidentified virus cultured from faeces. Full, rapid recovery
6	M.	61	Nov. 1968	3 days	Radiculopathy (neuralgic amyotrophy)	Partial recovery only. 1969-70: cerebral atrophy
7	F.	40	Sep. 1969	2 hours	Encephalopathy	C.S.F.: 50 and 75 mg protein/100 ml

An oil adjuvant influenza virus vaccine was given to each patient.

Recovery began within a week. Steroid therapy was not used. When he left hospital on 5 December he was able to walk unaided but had signs of a residual paraparesis. By February 1964 the signs had returned to normal despite his complaint that his left leg felt wooden. At his final examination on 8 July 1964 he was well and without symptoms, his knee and ankle jerks remaining sluggish. He left South Wales at this time but has recently written that he remains well and has had no recurrence of his symptoms.

Case 8

In the previous five years this 26-year-old pharmaceutical representative had been vaccinated four times against influenza without untoward effect. On 19 September 1970 he was given a new preparation, similar to that used in Case 1, but with different strains of A and B viruses.† Two days later he felt ill and nauseated and was sweating profusely. His temperature was normal. Symptoms persisted for several days, clearing up before the end of the week. On 5 October, or within the next day or two, he awoke with blurred vision of his left eye, being able to see the periphery but not the centre of an object. When he failed to see the shuttlecock at badminton, a game at which he excelled, he consulted his optician and was subsequently referred to hospital on 20 October.

Abnormal signs were restricted to his visual system. The acuity of the right eye was 6/4, and the fundus and field were normal. On the left side the acuity was approximately 6/24, the optic disc was swollen, and the retinal veins were very distended with many perivenous haemorrhages. The left field showed a central scotoma with scattered smaller defects. Occlusion of the central retinal vein was diagnosed.

Investigations, including repeated blood counts, liver function tests, Wassermann reaction, Reiter protein complement fixation test, and x-ray examination of chest, skull, and optic foramina, were all normal. Lumbar puncture and electroencephalogram were normal, and culture of faeces and spinal fluid for virus was negative. Virus complement fixation tests, including influenza A and B, showed titres < 1/8 on 20 October, 30 October, and 8 December. The results of haemagglutination-inhibition tests were as follows: 20 October—A2 HK 1/320, and B 68 1/160; 8 December—A2 HK 1/160, and B 68 1/160; 23 March 1971—A2 HK 1/40, and B 68 1/40.

The differential Paul-Bunnell-Davidsohn test was performed twice as follows: 30 October—saline 1/60, guinea-pig kidney < 1/10, and ox cells 1/80; 23 March 1971—saline 1/160, guinea-pig kidney 1/20, and ox cells 1/80. These results were reported as similar to the changes seen in serum sickness. (The patient had been given antitetanus serum on only one occasion, many years earlier. He did not recall any reaction to it.)

Therapy with prednisone began on 30 October 1970. In the

following months his vision steadily improved and by mid-April 1971 was virtually normal. He was conscious of very slight blurring at the centre of the left field, and a tiny haemorrhage was still visible at the macula. A month later both central and peripheral fields were intact. Recovery was complete.

Other Cases

Cases 2 to 7.—The salient features of these cases are recorded in the Table. Hypersensitivity to egg protein was the probable cause of encephalopathy in one patient (Case 7) whose symptoms began within two hours of vaccination. Encephalopathy which began 24 hours and four days later was the diagnosis in two schoolboys, one of whom (Case 3) died, the other (Case 5) making a rapid recovery. Improvement was slow or partial in a woman (Case 4) with transverse myelopathy and in two men (Cases 2 and 6) with peripheral nerve disorders.

Case 9.—Dr. Homann's patient, a woman aged 45, developed pain and paraesthesiae in both lower limbs 10 days after vaccination on 8 November 1969. Two months later she was no better.

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†A2/HK/X31/68, 400 IU; B/England/5/66, 200 IU.