Current Surveys

COMPLICATIONS OF SMALLPOX VACCINATION

E. H. BROWN, D.M., M.R.C.P., D.C.H.

Consultant in Infectious Diseases
Hiher Green Hospital
London, S.E.13.

IN RECENT years the policy for smallpox vaccination has again come under review and much of the controversy hinges around the frequency and nature of the more serious complications, especially in relation to the nervous system. From 1948 Medical Officers of Health of the Local Health Authorities in England and Wales were requested to send reports to the Ministry of cases of generalised vaccinia, post-vaccinal encephalomyelitis and deaths from other complications. This has been the subject of a recent review (Conybeare, 1964) covering the period 1951-1960. Apart from the deaths it is unlikely that these reports are complete as shown for example that only sixteen cases of eczema vaccinatum were reported, whereas Copeman and Wallace (1964) recorded 185 cases in the first few months of 1962 during the mass smallpox vaccination in England and Wales.

The complications may be broadly divided into those characterised chiefly by cutaneous manifestations and those involving the nervous system.

Cutaneous Complications

1. *Secondary bacterial infection.* These have been few in number since the introduction of glycerinated calf lymph in 1899 (sheep lymph since 1947).

2. *Auto inoculation.* By means of scratching, an active lesion may produce secondary pocks over various parts of the body, or by accidental inoculation on to another individual. They may appear by successive inoculation over a period of 9 days between the first inoculation and the achievement of insusceptibility (yet all come to maturity at the same time). This complication is not serious except when the eye is involved, but may lead to disfiguring scars.

3. *Toxic eruptions.* These are mainly of the erythema multiforme type and occur 7-10 days following vaccination (sometimes up to the 14th day). The eruption may be generalised or localised to a particular area, usually cause little constitutional disturbance and clear within 3-5 days.

Other conditions described (Sarkany and Caron, 1962) include toxic erythema, erythema nodosum, lesions simulating granuloma annulare, pityriasis rosea and eczema. As the number of cases reported are few and have occurred up to 8 weeks after vaccination (average $3\frac{1}{2}$ weeks) it seems likely that many of these are coincidental or the vaccination merely a predisposing factor.

4. *Generalised vaccinia.* (a) *Mild generalised vaccinia.* Although a number of these cases are reported, and auto-inoculation unlikely by reason

of the distribution or for other reasons, there is some doubt whether it exists, and they may be varicella or other causes (including post-inoculation vaccinia).

(b) *Eczema vaccinatum.* This is a serious condition due either to vaccination of an individual with eczema or accidental inoculation by contact with inoculated siblings or others. At the least, unsightly scarring may result, but some cases are fatal (most of the deaths are under two years). The origin of the rash is haematogenous and may occur between 5 and 14 days after primary vaccination. The more severe forms are characterised by high pyrexia, marked toxicity and an extensive vesicular and pustular eruption chiefly confined to the areas of eczema. Anti-vaccinal gammaglobulin is probably worth giving when the case is first seen and in the most severe cases N-methyl-isatin- β -thiosemicarbazone (methisazone) has been tried but without obvious effect.

(c) *Progressive vaccinia (vaccinia gangrenosa).* A rare and highly fatal complication associated with hypo- or a-gammaglobulinaemia. These patients lack plasma cells which are responsible for the synthesis of antibody and gammaglobulin. The initial vaccinal lesion fails to heal and progresses to involve more and more areas of adjacent skin, and the necrosis of tissue continues over a period of months. Metastatic lesions may develop in other parts of the skin, bones or other viscera. This condition may be suspected in children who have suffered from repeated pyogenic infection of the skin, respiratory tract or urinary tract. These rare cases usually occur in infancy and show little response to post-vaccinal gammaglobulin, methisazone, lymphatic tissue transplants etc. and progress to a fatal outcome over a period of weeks or months.

Neurological Complications

The first autopsy of post-vaccinal encephalomyelitis was that observed by Turnbull in 1912. A wave of post-vaccinal encephalomyelitis started in Europe in 1922 reaching a maximum in 1930. The obscure features are (a) why it had not been described before this, and (b) the wide variation in incidence between different countries (more common in Holland, Germany and England) and also between various districts of the same country and from year to year.

No association has been established between any of the other known virus infections of the central nervous system and experience with mass vaccination in recent years in this country suggests

that the incidence is lower now. There is no evidence that the method of vaccination or the type of lymph used affects the incidence. Of the encephalitic complications, encephalomyelitis does not occur under 2 years, and encephalopathy is a feature of this age group as well as in older children (De Vries, 1960).

1. Post-vaccinal encephalomyelitis.

The incubation period is 8-15 days and occurs only after vaccination of the non-immune (whether primary or revaccination after a long interval). The usual manifestations are fever, headache, vomiting, meningitic signs, paralyses, drowsiness, coma or convulsions. The CSF usually shows an increase in cells (lymphocytes) and increased protein; the EEG shows generalised high-voltage slow waves from both hemispheres. If the patient recovers recovery tends to be complete. Post-vaccinal encephalomyelitis has been thought to be an auto-immune reaction in which the chief target organ is the white matter of the central nervous system. The post mortem histology shows perivenous microglial proliferation involving the white matter of the cerebral hemispheres and the grey and white matter of the brain stem.

2. Encephalopathy (infancy and in childhood).

The incubation period is 2-18 days (usually about 8 days) and the onset is often abrupt with high fever, convulsions and perhaps hemiplegia and aphasia. Spinal cord involvement does not occur. Cerebral oedema and vascular lesions probably play a part and the CSF is normal (protein may be increased).

Infants (and young children) are susceptible to a "toxic encephalopathy" from almost any form of viraemia if it is severe and prolonged and improvements in techniques of virus isolation have made it possible to show (Apostolov, Flewett and Thompson, 1961) that the viraemia consequent upon primary vaccination in a very young infant may be overwhelming and rapidly fatal, almost the only post-mortem change in the brain of such cases being cerebral oedema. This distinction between encephalomyelitis and encephalopathy may, however, prove to be a different response of the human brain at different stages of its development to a similar etiological cause.

Out of 64 cases of central nervous system illness associated with vaccination during the period 1951-1960 (Conybeare, 1964) there were 22 deaths. Seventeen of these occurred out of 40 cases under one year, and it is especially in this age group that some of the deaths may be wrongly attributed to vaccination.

Treatment. No specific measures are available. In encephalomyelitis (as in cases following certain other virus infectious diseases) which popular belief attributes to an allergic response to the virus, it is common practice to use corticosteroids. But in infectious diseases units, where probably the largest numbers are seen, some doubts have been expressed as to their value in a disease of

such varying course. Some support for this is given by Boe, Solberg and Saeter (1965) in a retrospective study of 346 cases of acute meningoencephalitis. Ninety-one of these were post-infectious (measles, rubella, varicella and mumps) with a mortality of 32% which, however, is considerably higher than seen in this country. No one individual sees sufficient cases following vaccination to give comparable experience.

3. Other nervous system findings.

Meningism at the time of the acute febrile response has been noted. Polyneuritis has also been reported and this is not surprising as it does occur rarely after some of the common virus infectious diseases e.g. varicella, rubella, etc.

Other Complications

Rarely bone involvement has been described. Virus involvement of bone is rare and only smallpox and vaccinia are known to affect bone tissue in man.

Comment

It was on the basis of Wynne Griffith's figures (1962) that it was recommended that vaccination carried less risks in the second year than the first year of life, but these figures are probably unreliable. Many sudden and unexpected deaths occur in infancy and not all the deaths reported as due to vaccination have been properly substantiated. Avoidance of the first year will certainly avoid some of these cases and also those due to progressive vaccinia (child will have died or condition recognised by this time). If more information is to be obtained concerning neurological complications a detailed survey is needed with adequate investigation of all cases as they occur. Until we know more about the cause of encephalomyelitis and encephalopathy it is impossible to say whether the use of an inactivated vaccine will reduce this hazard, but perhaps eradication of smallpox from endemic areas will render smallpox vaccination no longer necessary as a routine procedure in others part of the world.

REFERENCES

- APOSTOLOV, K., FLEWETT, T. H., THOMPSON, K. S. (1961): Death of an Infant in Hyperthermia after Vaccination. *J. clin. Path.*, **14**, 196.
- BOE, J., SOLBERG, C. O., SAETER, T. (1965): Corticosteroid Treatment for Acute Meningoencephalitis: A Retrospective Study of 346 cases, *Brit. med. J.*, **i**, 1094.
- CONYBEARE, E. T. (1964): Illness attributed to Smallpox Vaccination 1951-60 Mon. Bull. Minist. Health, Lab., Serv., Vol. 23., Part I 126, Part II 150, Part III 182.
- COPEMAN, P. W. M., WALLACE H. J., (1964): Eczema Vaccinatum, *Brit. med. J.*, **ii**, 906.
- GRIFFITH, G. W. (1962) in 'Smallpox,' C. W. Dixon, London: J. and A. Churchill.
- SARKANY, I., CARON, G. A. (1962): Cutaneous Complications of Smallpox Vaccination. *Trans. St. John's Hosp., derm. Soc. (Lond.)*, **48**, 163.
- VRIES, E. de (1960): Post-vaccinal Peri-venous Encephalitis. Amsterdam: Elsevier.