CORRESPONDENCE

Correspondents are asked to be brief

Measles Vaccination and Tuberculin Test

SIR,—I would like to draw attention to an occasional sequel to measles vaccination which is not, I believe widely, known—namely, the temporary conversion of a positive tuberculin reaction to a negative one. That this may be of importance is illustrated by the following case.

A girl aged 1 year and 9 months was admitted to hospital on 1 October 1971 with a history of otitis media which had failed to respond to four days' antibiotic treatment. The diagnosis was confirmed, but despite continued treatment the child remained unwell. Eleven days after admission there was sudden deterioration and tuberculous meningitis was diagnosed on the cerebrospinal fluid findings. Acid-alcohol-fast bacilli were seen in the smear and the culture subsequently became positive. The chest x-ray remained clear throughout the illness, but despite treatment she died two months after diagnosis. Late diagnosis in this case contributed substantially to the fatal outcome, and one of the misleading findings was negative tuberculin tests, the tine test (5 October), Heaf test (15 October), and Mantoux test (1/1,000) (18 October) all being negative, though the 1/100 Mantoux test on 25 October was positive. The child had been given measles vaccine in the middle of August, approximately six weeks before her first attendance at hospital, and her mother volunteered retrospectively that she "had not been really well" since then.

Von Pirquet[1] reported in 1908 that a positive tuberculin skin test may become negative during measles, and in the days when primary tuberculous infection commonly occurred during childhood this fact was well recognized. Measles in a child with a primary infection was also believed to predispose to miliary tuberculosis or tuberculous meningitis. The present patient had no known contact with tuberculosis. Necropsy showed a small calcified focus in the right upper lobe with consolidation. There was no enlargement of hilar nodes and no generalized spread such as might account for a negative, or only weakly positive, tuberculin skin test. It seems likely that measles vaccination had resulted in a state of temporary anergy—that is, the effect was like that of an attack of measles, although there were no symptoms of measles.

In the Report of the First International Conference on Vaccines against Viral and Rickettsial Diseases in Man held in 1967 Dr. Coriell quoted the recommendation of the American Academy of Pediatrics that, where a tuberculin skin test is to be performed at approximately one year, it should be performed before measles vaccination so that positive reactors can be treated. He went on to say that "obviously the test should not be done after measles vaccination since the latter will create tuberculous anergy in a certain number of cases which may persist for a month or longer." He also referred to three cases of tuberculous meningitis which had occurred three to four months after vaccination.

Measles vaccination is obviously of immmense potential benefit to the child population, but possible adverse effects under special circumstances should be borne in mind, particularly in view of the recent increase in childhood tuberculosis. There would seem to be a case for the Heaf testing of infants with known tuberculosis contacts before giving the vaccine and for considering tuberculosis in the differential diagnosis of any child who becomes ill after measles vaccination.—I am, etc.,

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1 Pirquet, C. von, *Deutsche Medizinische Wochenschrift*, 1908, **34**, 1297.
2 Pan-American Health Organization, *First International Conference on Vaccines against Viral and Rickettsial Diseases*, Washington, Pan-American Sanitary Bureau, 1967.

Measles Vaccination and the Nephrotic Syndrome

SIR,—Reactions to measles vaccination are apparently few,[1] and guidance on its administration has been given by you.[2] It is therefore of interest that we have encountered two children who developed the nephrotic syndrome after vaccination.

Case 1.—In December 1971 a 21-month-old boy was immunized against measles. Nine days later he developed generalized erythema involving mostly the trunk and arms, swelling of the eyes, scrotum, and penis. He was treated with antihistamines and his rash abated within 48 hours, but he was noted to have peripheral oedema and ascites. His past history was negative except for eczema in his first year. He had been well for many weeks, had received no drugs, and had not been in contact with any infectious diseases. Investigations showed: Hb 12.6 g/100 ml; W.B.C. 14,300/cm,^{3} with neutrophils 61%, lymphocytes 36%, monocytes 3%. Platelet count was normal; E.S.R. (Westergren) 85 mm/1 hr; cholesterol 550 mg/100 ml; total protein 4.6 g/100ml, albumin 1.2 g/100 ml. Protein electrophoresis showed raised alpha-2 globulins and low gammaglobulins. Urine: massive proteinuria, mostly albumin.

The patient was treated with prednisolone, which was discontinued in June 1972. Since then he has been in remission.

Case 2.—A 4-year-old boy was admitted to hospital in October 1972 with relapsed nephrotic syndrome after acute follicular tonsillitis. Investigations showed: Hb 11.2 g/100 ml; W.B.C. 8400/mm^3—neutrophils 46%, lymphocytes 44%, monocytes 6%, plasma cells 4%. E.S.R. (Westergren) 90 mm/1 hr; cholesterol 215 mg/100 ml; total proteins 4.3 g/100 ml, albumin 1.6 g/100

ml. Protein electrophoresis showed an increase of alpha-2 globulin with a decrease of gammaglobulin. Urine: massive proteinuria, mostly albumin.

The patient was treated with antibiotics and prednisolone and responded well. He had been admitted to another hospital at the age of 2 years with typical features of nephrotic syndrome, which was confirmed by the appropriate investigations. He had received a course of prednisolone which was finally discontinued one year later. He had been in remission up to his present episode. Detailed inquiry showed that before his first admission to hospital he had been immunized against measles. Five days afterwards he became feverish and developed conjunctivitis, which did not respond to topical antibiotics, and three days later his mother noted generalized oedema and swelling of his eyes. During the first year of life he had had recurrent attacks of wheezy bronchitis for which he required bronchodilators. There was family history of bronchial asthma but not of other allergies.

These two children are atopic subjects who should not have had measles vaccination. Nevertheless, it is surprising that the nephrotic syndrome has not been reported previously. Possibly accurate medical histories were not obtained. If these observations can be substantiated by others, and since the nephrotic syndrome is not known to occur after natural measles, it would suggest that other factors in the vaccine are involved which might offer a useful line of research into the elucidation of the basic nature of this disorder.

Since these observations were made a third case similar to the above has been seen.—I am, etc.,

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1 Department of Health and Social Security. *Circular Letter* CM07/70 July, London, D.H.S.S., 1970.
2 *British Medical Journal*, 1968, **1**, 395.

Rubella Vaccination and Termination of Pregnancy

SIR,—There have been few reports from Britain of inadvertant rubella vaccination in pregnancy. For this reason the report of Drs. Hélène J. Mair and A. R. Buchan (4 November, p. 271) is important in that it draws attention to the problem and stresses that rubella vaccine should be given only to women who are seronegative, who are not pregnant, and who have been warned of the possible risk involved if they should become pregnant in the next two months. In my experience, inadvertent rubella vaccination during pregnancy is seen more commonly than is rubella in pregnancy. If this is generally so, then publishing national figures of abortions performed because of inadvertant rubella vaccination in pregnancy, as suggested by Drs. Mair and Buchan, would help to draw attention to the extent of this preventable iatrogenic disease.

The risks of rubella vaccination in pregnancy cannot be known until all cases of women being inadvertently vaccinated are carefully documented, the products of conception examined virologically, and any children born followed up for at least five to seven years for any signs of the expanded congenital rubella syndrome. The following figures from the world literature until October 1972 may help family practitioners and gynaecologists to advise patients who are vaccinated just before or during early pregnancy.

No cases of embryopathy due to rubella vaccine have been reported. Only three cases of fetal infection with rubella virus have been reported—attenuated rubella virus was isolated from the kidney (and from only the kidney) of one fetus,[1] from the femoral bone marrow (and from only the femoral bone marrow) of another,[2] and from the eye of another.[3]

In 60 women who were known to be seronegative before inadvertent vaccination just before or during pregnancy, or before vaccination in women who were to have legal abortions, [1 2 4-10] rubella virus was obtained from only two fetuses[1 2] and from the placenta or decidua of only seven.[1 8]

Of the 37 women known to have been seropositive before vaccination,[1 9] no virus was obtained from the products of conception of the 35 who had spontaneous or induced abortions, and the two babies born were described as being apparently normal.[9]

Of the 70 women whose immune status was not known before vaccination,[11 12] the virus was obtained from the placenta or decidua from two women. Histological lesions similar to those found in rubella were noted in the placentas from these two women and from one other patient.[11] It was reported that nine women were still pregnant and that the 10 babies already delivered were apparently normal.[12]

The United States Center for Disease Control[3] summarized the reports it had received until October 1971 of 193 women vaccinated in pregnancy. Because some of the cases listed above might also have been included with these, the figures are given separately. There were 171 women whose immune status was not known before vaccination. From the products of conception of the 97 of these who had spontaneous or induced abortions no virus was obtained. Of the remaining 74, 56 had delivered apparently normal live babies and 18 were still pregnant. Of the 22 women known to be seronegative before vaccination, rubella vaccine-like virus was found in the decidua or placentas of three, and in one of these cases the virus was isolated from the eye of the fetus.[3] Eight had delivered apparently normal babies and one was still pregnant.

None of the babies born to mothers who were vaccinated during pregnancy showed evidence of the congenital rubella syndrome; reports of the births of 64 such babies have been made by the United States Center for Disease Control,[3] of 38 by Gold,[13] of 10 by Cooper,[12] and of another 10 by others.[9 11 14 15]—I am, etc.,

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1 Vaheri, A., *et al.*, *New England Journal of Medicine*, 1972, **286**, 1071.
2 Ebbin, A. J., *et al.*, *Lancet*, 1972, **2**, 481.
3 Center for Disease Control, *Rubella Surveillance*, United States Department of Health, Education and Welfare, Atlanta, Georgia, October 1971, No. 3, p. 12.
4 Prinzie, A., Huvgelen, C., Gold, J., Farquhar, J., and McKee, J., *American Journal of Diseases of Children*, 1969, **118**, 172.
5 Furukawa, T., *et al.*, *American Journal of Diseases of Children*, 1969, **118**, 262.
6 Katz, S. L., *American Journal of Diseases of Children*, 1969, **118**, 317.
7 Halonen, P., *American Journal of Diseases of Children*, 1969, **118**, 317.
8 Phillips, C. A., Maeck, J. Van S., Rogers, W. A., and Savel, H., *Journal of the American Medical Association*, 1970, **213**, 624.
9 Bolognese, R. J., *et al.*, *American Journal of Obstetrics and Gynecology*, 1972, **112**, 903.
10 MacDonald, H., Thompson, K. M., and Tobin, J. O'H., *Practitioner*, 1971, **207**, 57.
11 Larson, H. E., Parkman, P. D., Davis, W. J., Hopps, H. E., and Meyer, H. M., *New England Journal of Medicine*, 1971, **284**, 870.
12 Cooper, L. Z., *Canadian Journal of Public Health*, 1971, **62**, (September Monograph Supplement), p. 48.
13 Gold, J., *Canadian Journal of Public Health*, 1971, **62**, (September Monograph Supplement), p. 68.
14 Chin., J., Ebbin, A. J., Wilson, M. G., and Lennette, E. H., *Journal of the American Medical Association*, 1971, **215**, 632.
15 Editorial Comment, *Obstetrical and Gynaecological Survey*, 1971, **26**, 235.

SIR,—I would like to record a further three cases of rubella vaccination during pregnancy in support of the recommendations of Drs. Hélène J. Mair and Alan R. Buchan (4 November, p. 271).

In the first case the nature of the vaccine had been misunderstood and it was administered to a patient known to be eight weeks pregnant because she had been in contact with a case of rubella. As soon as the error was discovered the patient was referred for termination and the conceptus was aspirated at 10 weeks. No virus was isolated from either placental or fetal tissue which was submitted for examination. In the second case the patient became pregnant six weeks after rubella vaccination. Aspiration of the conceptus was performed at eight weeks and again no virus was isolated from the products of conception. The third case was estimated to have conceived 60 days after administration of the rubella vaccine and it was decided to allow the pregnancy to continue. The patient has subsequently given birth to an apparently normal child.

The virological studies were kindly performed by the virus diagnostic laboratory at the Preston Royal Infirmary.—I am, etc.,

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Exposure to Rubella in Pregnancy

SIR,—Sometimes a pregnant woman is exposed to infection from rubella in her own child. Maternal concern is such that blood is often taken within 14 days of the earliest possible date of infection—that is, within too short a time for antibodies to appear as a result of infection from the child.[1] Should antibodies be found it is rightly concluded that there had been no risk from the child, since immunity had already been established. But there are two other possibilities: (1) the mother may have had a subclinical infection and passed on the virus to her child, who then developed the full clinical picture; (2) mother and child may have been infected from the same source. There is all the more reason to think of these possibilities when the child is so young that probably it has met with others only when with its mother.

An 18-month-old girl was seen with what was considered to be typical rubella. Her mother, aged 22, was 18 weeks' pregnant. She gave a precise history of having herself suffered twice from rubella as a child. Notwithstanding, on the second day of the child's rash the doctor took blood from the mother. This was found to have antibodies at the upper limit of the routine test used in the laboratory. The serum was therefore retested, using a higher range of dilutions. The titre which emerged was, in the light of the experience of the laboratory, thought to be suggestive of fairly recent infection. At no time did