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Pointers

Intrauterine Transfusion: Workers in Newcastle concluded from their studies that in spite of the hazard this procedure has an important role in the management of some cases of Rh-haemolytic disease (p. 189).

Transepidermal Water Loss: Is greatly increased in patients with erythroderma, psoriasis, and ichthyosis compared with normal subjects. This may explain the hypothermia and increased B.M.R. found in some of these patients (p. 195).

Emergency Intracardiac Pacemaking: Discussion of bedside method of placement using intracavitary electrocardiogram picked up by pacemaker electrode as a guide in patients with Adams–Stokes attacks (p. 199).

Oxygen Therapy: In paediatric use knowledge of exact concentration of oxygen is important. Studies show that incubators generally fulfil manufacturers' specifications, and that the Oxygenaire Humidaire Tent was the most efficient of the tents tested (p. 201).

Colitis in India: Ulcerative variety is not rare, but diagnosed less often than in the West because of the frequency of infectious conditions of the bowel, lack of facilities for precise diagnosis, and lack of long-term follow-up (p. 204).

Congenital Cyanotic Heart Disease: Retinal vascular changes initially present revert to normal after surgical correction of cardiac lesion, but E.E.G. defects do not change because they are not due to simple cerebrovascular disturbance (p. 207).

Electrophoretic Studies and Cancer: Study of survival of radioiodine-labelled serum γG-globulin showed that the different fractions broke down at different rates, and were different in a patient with cancer from a normal subject (p. 210).

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Prophylaxis in Rubella

Since the recognition of the teratogenic properties of rubella virus a quarter of a century ago many attempts have been made to prevent the disease during the early months of pregnancy. Until recently the only practical method of prevention has been by passive immunization. The results of 25 years' experience with either convalescent plasma or serum, pooled gammaglobulin, or convalescent rubella gammaglobulin have recently been reviewed by R. Lundström.[1] In experimentally induced infections gammaglobulin was surprisingly ineffective,[2] while in clinical trials the degree of protection afforded by this form of prophylaxis showed wide variation, though in a number of studies a substantial degree of protection was shown.[3-6]

Several factors probably contribute to the disappointing results reported with gammaglobulin in the prevention of rubella compared with its more obvious effect against measles. It is clear from the data reviewed by Lundström that the results were in many instances based on a small number of individuals, of different age and sex, living under widely differing environmental conditions and subjected to varying degrees of exposure to rubella. From 1954 to 1963 there was no practical method of assaying the content of rubella antibody in the prophylactics. Dosage could be an important factor in determining the outcome, as it is known that the antibody content can vary from batch to batch.[7 8] The time of administration is probably even more important in view of the newly discovered details of the pathogenesis of rubella and in particular the prolonged period of infectivity and presence of viraemia, both of which occur for several days before the onset of the rash. More important, however, is the fact that the assessment of the efficacy of gammaglobulin in rubella on the basis of clinical attack-rates is not very meaningful when so many infections are atypical or subclinical. Subclinical infection may be associated with viraemia and foetal damage,[9] and the trials so far reported have not established whether gammaglobulin, which has been shown to reduce the clinical attack-rate, protects the foetus, or what is the true rate of infection in immunized persons who do not develop symptoms. Some of the answers to these problems were contained in two papers in the *B.M.J.* of 9 September.[10 11]

Since 1954 gammaglobulin has been available to general practitioners in this country. In an earlier report J. C. McDonald[5] showed that the clinical attack-rate in family contacts given 750 mg. or 1,500 mg. of gammaglobulin was 1.27%. In a group of untreated women observed at about the same time the attack-rate was 3.7%.[12] This suggested that the gammaglobulin had a protective effect, but the attack-rates were low in both groups and the two were not strictly comparable. Now McDonald and C. S. Peckham[10] report a further study on the use of gammaglobulin and its possible protective effect on the foetus. During the period 1954–62 gammaglobulin was issued to 36,577 rubella contacts. The dosage varied from 750 mg. to 1,500 mg., depending on the availability of supplies.

Data were finally obtained on 30,764 contacts, of whom 370 (1.2%) developed rubella within 28 days of inoculation and a further 0.3% at intervals thereafter. Later in the epidemic the attack-rate rose from 1.2% to 2.5% and then to 3.25%. The overall attack-rate in 15,173 women exposed to family contacts was 1.95%. As with the earlier survey this seems a low figure, but it is not possible to tell what it would have been without gammaglobulin. Attack-rates of 12% to 30% in unprotected women have been reported in surveys elsewhere. The observations on the incidence of defects, however, are more enlightening. Six hundred and ten women developed rubella and 424 (70%) came to term, including 319 cases of failure of prophylaxis and 105 cases in which the mothers had been treated with gammaglobulin after the appearance of the rash. Of the 424 liveborn children observed at the first postnatal inquiry at 3–9 months of age, 13% were found to have defects, of which 9.2% were of the rubella syndrome type. At the second postnatal inquiry at 2 years of age the rates increased to 18% for total defects and 13.6% for rubella defects, mainly heart disease and deafness in various combinations. No cataracts were observed, but only 14% of the 424 women were exposed in the first eight weeks of gestation.

The incidence of defects in the 30,297 women who were in contact with rubella but who escaped infection was very different. Information was obtained from all but 13%. At the first postnatal inquiry 2.6% were found to have congenital defects, of which 0.4% were of the rubella type, with 3.6% and 0.6% at the second inquiry. The type of defects were very different from those observed in the offspring whose mothers had had rubella. They consisted in the main of malformations of the central nervous system and the musculoskeletal and cardiovascular systems—malformations that are to be expected in the normal course of events. Comparatively few cases of deafness were encountered and a difference was also noted in the incidence of patent ductus arteriosus in the two groups. This latter manifestation is commonly associated with congenital rubella and is usually found together with other rubella-type defects. Eleven cases of patent ductus were observed out of 93 (11%) cases of congenital heart disease in the group who escaped infection, compared with 8 out of 13 cases (62%) in the group whose mothers had had rubella. Thus there was no excess of rubella-type defects in this group as a whole. This in itself is an important finding; but what could not be determined was the actual number of women in contact with rubella who did not develop clinical disease and who escaped infection altogether. This, after all, is the real test of the prophylactic value of gammaglobulin.

Antibody tests for rubella have recently been developed, and these have been used by members of the Public Health Laboratory Service to study the matter in more detail. In a report prepared by D. N. Hutchinson and his colleagues[11] it was found that only 4.9% of pregnant women in the Manchester area did not possess rubella neutralizing antibody. This is a low figure, but it is known that the incidence of rubella antibody varies considerably from one population group to another.[13 14] In further studies in six different areas in the Midlands and north-west the proportion of non-immune subjects was found to vary from 6% to 21%. In 30 non-immune contacts given 750 mg. of gammaglobulin, 26.7% showed evidence of infection with production of antibody (seroconversion), and in 29 contacts given an additional 1,500 mg. between 8 and 12 days after contact 31% showed seroconversion. All but one of the patients showing evidence of infection received an initial dose of gammaglobulin within three days of contact. This study also showed once again the very much higher risk from contact in the home than elsewhere. A quite marked variation in antibody titre was detected among the 16 batches of gammaglobulin, but the numbers of susceptibles receiving material from any one batch was too small for differences in protection to be determined. These results indicate that the true attack or infection rate is around 30%.

Despite the obvious shortcomings of gammaglobulin revealed by these studies it still has a role as a prophylactic, limited though it may be. With the development of the haemagglutinin-inhibition test for rubella,[15] which is quicker and more sensitive than the neutralization test, it should be possible to study the problem further by concentrating on the use of gammaglobulin of high titre given to non-immune contacts with the minimum delay after exposure. The main difficulty in studying rubella is inherent in the natural history of the disease. Infected individuals can be shedding virus for such a long and variable time before the onset of symptoms —and for a comparable time in subclinical infections—that it is difficult to determine when first contact has occurred. These and other results point to the need for the development of a rubella vaccine. Progress has already been made in this direction. P. D. Parkman and his colleagues[16] have reported preliminary findings with an attenuated rubella vaccine prepared in monkey kidney-cell cultures which produced seroconversion without symptoms of infection in vaccinated children, though a number were found to be excreting virus from the oropharynx, albeit in low titre. Since this report further vaccines have been developed and are now on trial in several areas.[17] Special problems of safety and antigenicity have to be considered in the development of a rubella vaccine, and it is likely to be several years before such a vaccine could be put into general use. Nevertheless, great progress has been made in a very short time.

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