

RUBELLA

ETHELWALD E. VELLA

PH.C., B.Sc., M.D., F.R.C.PATH., M.I.BIOL.,
D.C.P., D.T.M.&H., L/R.A.M.C.

*Assist. Professor of Pathology,
Royal Army Medical College, London.*

Originally physicians did not and indeed could not make an accurate distinction between the various fever-with-a-rash syndromes such as measles, scarlet fever, typhus and so on, but about 200 years ago various medical papers written by German authors described one such fever-with-rash entity which was most commonly referred to as R \ddot{o} theln and subsequently became more generally and more popularly known as German measles, precisely because of these geographical and historical antecedents.

R \ddot{o} theln one must admit is a typical teutonic word, harsh to our unaccustomed ears, requiring good coordination on the part of our tongue, lips and larynx to enunciate; towards the latter half of the last century the army surgeon Veale writing in the *Edinburgh Medical Journal* (1866) stated 'the attention of the medical profession has occasionally been directed of late years to the occurrence of a peculiar form of eruptive disorder which has certain points of resemblance both to measles and to scarlet fever, and which

would appear to stand nosologically about midway between them. In Germany it has been regarded as a distinct disease and has received the name of R otheln. The name of a disease is always a matter of some importance. It should be short for the sake of convenience in writing, and euphonious for ease in pronunciation. I therefore venture to propose Rubella as a substitute for R otheln.'

And so Rubella it has been ever since.

It affected mostly children, it had a certain nuisance importance when it interfered with the parents' social and childrens' educational programmes but no great importance was attributed to it. A *laissez-faire* attitude prevailed until some time during World War II, (it is of interest to observe that three of the six biggest epidemics so far in this century occurred during World War I, World War II and the Korean War), when from Australia strange hard-to-believe stories about the teratogenic effects of Rubella were being discussed and recorded by, somewhat unexpectedly, eye specialists.

Norman McAlister Gregg (later Sir Norman) was the prime mover in this new field. 'In the first half of the year 1941 an unusual number of cases of congenital cataract made their appearance in Sydney. Their frequency, unusual characteristics and wide distribution warranted closer investigation'. Gregg duly observed and reported cataracts, micro-ophthalmia, nystagmus, retinopathy, corneal clouding; what resounds perhaps even more to his credit he also recorded accompanying patent ductus arteriosus, congestive heart failure, low birth weights, feeding difficulties and even an abnormally high death rate in these unfortunate infants. 'The remarkable similarity of the opacities in the lens, the frequency of an accompanying affection of the heart and the widespread geographical incidence of the cases suggested that there was some common factor in the production of the diseased condition. The question arose whether this factor could have been some disease or infection occurring in the mother during pregnancy which had then interfered with the developing cells of the lens. By a

calculation from the date of the birth of the baby it was estimated that the early period of pregnancy corresponded with the period of maximum intensity of the very widespread and severe epidemic in 1940 of German measles'.

Two years later Gregg added: deaf-mutism, dental defect and mental deficiency to abnormalities caused by Rubella. His observations were fully corroborated by many investigators after he had shown the way, though not without the usual scepticisms of doubting Thomases; even "The Lancet" (1944) at one time doubted the correlation of children's malformations with Rubella of pregnant mothers, implying in an Editorial annotation that it was surely very unlikely that such reputedly obvious and serious complications of an infectious fever in pregnancy could have been missed even by the non-medical world.

Still Gregg had the satisfaction before he died in 1966 of seeing his views accepted and his observations confirmed in all countries wherever scientific medicine is practised.

The next most significant advance in the history of Rubella, nothing less in fact than the successful isolation of the etiological virus agent itself in the laboratory, circa 1962, is linked with the name of Walter Weller.

Weller and Neva, from the Harvard School, showed that infectious material containing the virus, when inoculated in tissue cell cultures, using cells obtained from the amnion of human placentas, produced visible evidence of the presence of the virus by certain easily detectable morphological changes in the appearance of the infected amnion cells, upon prolonged incubation for 3-5 weeks: 'Viruses apparently not heretofore described, have been isolated from the urine or blood of 4 patients with rubella-like illnesses. These agents were serially propagated in primary human amnion cultures and produced unique cytopathic changes characterised by the aggregation of nuclear material and the presence of inclusion bodies'.

At the same time and working independently a group of workers at the world



(Photo courtesy of the Wellcome Trustees)

Sir Norman McAlister Gregg the Australian ophthalmologist who first showed the teratogenic effects of Rubella in Pregnancy.

famous U.S. Army research establishment, the WRAIR (Walter Reed Army Institute of Research) succeeded in showing that the rubella virus could also invade and infect simian cells obtained from the kidneys of a certain species of monkey — the African Green Monkey. In these infected monkey kidney cell cultures it was not possible to detect a morphological change as compared with the cytopathic effects (CPE) obtained in human amnion cells. Nevertheless there was a biological change, as proof of virus infection could be demonstrated within 7-10 days by the mutual exclusiveness of 2 simultaneous virus infections; thus the rubella-virus infected but visibly unaffected simian cells when subjected to an attempted superinfection by another species of virus were fully refrac-

tory to the second invading virus. This is the 'interference' phenomenon, 'During February and March 1961, a new agent was isolated repeatedly from military recruits hospitalised at Fort Dix, N.J. This agent recovered from throat washings has been found to propagate only in a limited number of cell lines. In these it fails to produce cytopathologic effect (CPE). It is recognised only by its ability to interfere with ECHO virus, Type II.'

It is not always easy even in this day and age to diagnose clinically patients suffering from Rubella. There are many diseases which can simulate closely the picture of Rubella, there are many more sub-clinical infection than frank cases — the "iceberg" phenomenon seen in so many other infectious diseases, and there are

many mildly infected patients who exhibit no rash at all.

The successful isolation of the virus described above not only produced the only truly accurate method of diagnosis by isolation of the causative organism but also provided the means by such viral antigens could be produced in good amounts for the four serological tests used in laboratory diagnosis:

1. HAI — Haemagglutination Inhibition
2. CFT — Complement Fixation
3. Immuno-fluorescence
4. NT — Neutralisation.

Of these tests the one which is more familiar to most of us and which is in commonest use in most diagnostic laboratories is the HAI; it came into prominence about 3 years ago as the result of the work of Stewart and other investigators of the U.S. Public Health Service, "The haemagglutination inhibition test developed in this laboratory provides a simple, rapid and inexpensive procedure for use in the diagnosis of rubella, in determining status of rubella immunity and in testing the efficacy of experimental rubella-virus vaccines".

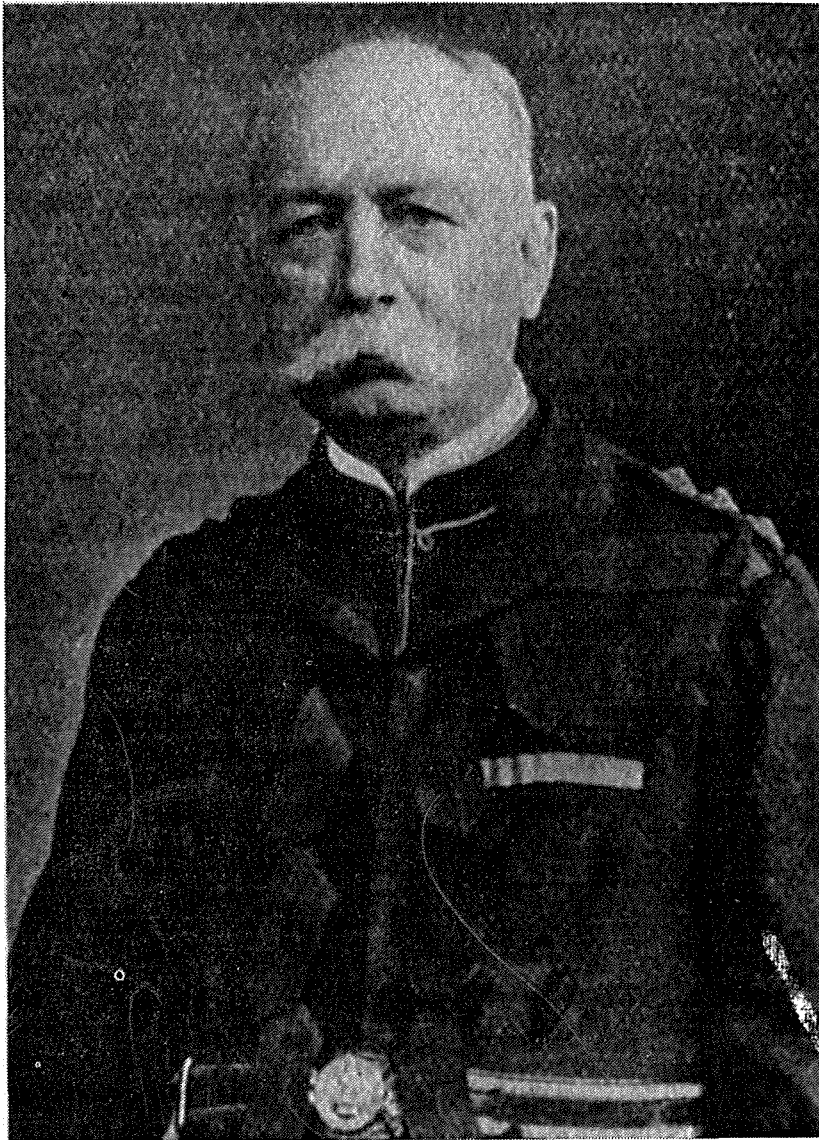
In this test the natural property of the rubella virus to agglutinate chicken cells is utilised to detect the presence or absence of anti-rubella antibodies in a patient's serum and thus indirectly to confirm or refute a suspicion of rubella infection. If a patient is infected with the rubella virus his or her serum will contain antibodies which will inhibit this characteristic property of the virus to agglutinate red cells on mixing the three reagents (Rubella virus × Fowl-cells × Patient's serum) together; if the patient is however suffering from some disease other than rubella his serum would possess no specific antibodies against the rubella virus and therefore on mixing the 3 reagents (virus × cells × serum) the uninhibited virus will now actively agglutinate the fowl cell.

This HAI test has proved very useful also in screening individual patients for evidence of past infection, for if a pregnant mother possesses antibodies to rubella (i.e. HAI is positive) as evidence of

a past infection with rubella, she can be reassured that no harm will result to her baby as a result of her coming into contact with a case of rubella; conversely in girls and women of child-bearing age the complete absence of antibody represents a real danger that if they get accidentally exposed to rubella when they eventually conceive, they will give birth to a congenitally malformed child, if their child is born at all. For some unknown reason this last observation does not seem to apply as much to Japanese women as to their western sisters.

The second and undoubtedly even more beneficial effect which resulted from the successful culture of the virus was the possibility of manufacturing suitable vaccines. The efforts of research workers in this field were no doubt spurred on by the rubella epidemic of 1963-64 which left thousands of children maimed in its wake and thus provided a great impetus towards the production of an effective prophylactic vaccine to protect susceptible individuals. This has recently become a real possibility at least in well-to-do countries. Present day vaccines contain a live virus which has been however so weakened by artificial culture in the laboratory that it can no longer produce its pathological effects while nevertheless retaining sufficiently its identity as a foreign agent when injected so that antibodies are produced in the vaccines which are almost as high in titre and possibly as persistent as those which follow natural infection.

For purpose of vaccine production the rubella seed virus is grown in one of four kinds of tissue cells obtained from: Monkey Kidney, Rabbit Kidney, Duck Embryo, Human Embryo, and thus in the relevant literature the reader comes across such hieroglyphics as HPV-77 which stand for a vaccine prepared from a virus which has been weakened by being cultured and subcultured at roughly weekly intervals for 77 times on monkey kidney cells. The first vaccine marketed in the U.S.A. (Merck's) bore the formula HPV-77 DE 5 — meaning that the virulence of the HPV 77 virus was still further attenuated by being serially sub-



The Army Surgeon Henry Richard Lobb Veale who first proposed the name Rubella.

cultured five more times on duck embryo cells. For various reasons duck embryo is a better medium for preparing rubella vaccine than chicken embryo. Another American vaccine called RA-27/3 and prepared in human fibroblast diploid cells is interesting in that it can be dispensed intranasally by nose drops or spray — a route

of vaccination which cannot be employed when using the other rubella vaccines all of which have to be inoculated subcutaneously.

The fourth vaccine, and the one which is or will be more familiar to us in Europe is the Belgian vaccine prepared in rabbit kidney (3 passages in Green Monkey Kid-

ney, followed by successive cultures in rabbit kidney for 53 times — GMK 3 — RK 53), it is marketed by Smith, Kline and French and costs about a guinea per dose (0.5 ml).

What of the future? It is fortunate that vaccines have been made available this year; epidemics of Rubella seem to occur every 6 years or so; the last epidemic occurred in many countries during 1963-1965 so that one may expect an epidemic of Rubella in the next 24 months.

Previously human immuno-globulin was our standby in the passive prophylaxis of Rubella but considerable doubt has been cast on its effectiveness; not only was the usual dose of 750 mgm containing an unknown titre of specific rubella antibodies too small but unless the immuno-globulin was given within 24 hours of exposure it could not be really expected to prevent infection. Hence to all intents and purposes we have to rely on "Cendevax" vaccine.

A Rubella vaccination programme that is currently being recommended by the army medical department is as follows:

a) Pregnant mothers are screened for rubella antibodies by adding an HAI test to the usual battery of prenatal serologic tests. If the test proves negative an immediate post-partum vaccination is advised with instruction to the patient to avoid all possibility of conception for the following 2-3 months.

b) Non-pregnant females who request protection are first screened by an HAI test (about 80% of these would be expected to have a positive HAI test and hence would not stand in need of vaccination). If the HAI is negative vaccination is offered with the same precautionary medical advice as detailed in (a) above.

2. Girls between 11-14 years, that is in the prepubertal age and girls approaching school-leaving age who repre-

sent the next generation of parents, are offered vaccination without preliminary testing.

In general it may be said that though little or only very mild reactions are to be expected after "Cendevax" vaccines yet rubella vaccines are apt to give more undesirable side effects the older the vaccinee, hence the recommended procedures of giving these female teenagers vaccination without wasting time and money in the preliminary HAI testing which is done in the case of older women of whom 1 in 12 will be found to need vaccination; moreover this single procedure of direct vaccination, as against the two procedures of preliminary HAI testing followed when necessary by vaccination, avoids subjecting the girls to 2 needle jabs which is thought might discourage some of them from accepting vaccination.

It is to be noted that as the situation stands today the pregnant-to-be multipara is the main target needing priority in protection, as she runs the greatest risk of getting infected from her own children with whom she is in daily close contact; at some date in the not so distant future vaccination could with profit be offered to all children of either sex between the ages of 1 to 11 without preliminary HAI screening in an effort to eradicate German measles by mass immunisation on a national scale. It may be also feasible to include Rubella vaccine with other vaccines (Measles, mumps) used for the primary immunisation programme of infants and thus make it more acceptable since this procedure would neither entail an extra visit of the parent and child to a doctor nor require an additional exhibition of syringe and needle.

The duration of protection afforded by Rubella vaccination is not yet known, hence the need for booster doses is not yet excluded.