Papers and Originals**THE DIAGNOSIS OF RUBELLA**

BY

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For many years the condition originally designated "Rötheln" by two German physicians (de Bergan, 1752; Orlow, 1758) was regarded as a hybrid of measles and scarlet fever. Maton (1815) was the first to describe it as a separate disease entity, and Veale (1866), of Edinburgh, called it rubella. Contrary to general belief, the diagnosis of rubella can prove extremely difficult, and while in ordinary circumstances an erroneous diagnosis may be unimportant the possibility of congenital malformations has rendered accuracy of diagnosis vital in cases of early pregnancy. The diagnosis of rubella in the absence of an epidemic is difficult because of its close similarity to other diseases and the lack of a specific diagnostic test. Krugman and Ward (1954), when examining 30 children reported as having rubella, found themselves unable to confirm the diagnosis in any single instance. In this context, retrospective evidence of rubella can prove wholly fallacious. For instance, on this basis Swan *et al.* (1943) thought that approximately 80% of women developing rubella in early pregnancy would produce malformed infants. On the other hand, reports based on prospective studies (Fox and Bortin, 1946; Aycock and Ingalls, 1946; Lundström, 1952; Pitt, 1957) as well as the Ministry of Health survey 1951-60 (Manson *et al.*, 1960) show that the true incidence is in the region of 25%.

Present Investigation

Table I presents an analysis of cases referred with a diagnosis of rubella and admitted to the infectious diseases department of the Royal Free Hospital and to Coppett's Wood Hospital during 1955-62. Table II presents an

TABLE I.—Patients Referred to Hospital with a Diagnosis of Rubella

Year	No. of Patients	Final Diagnosis					
		Rubella	Measles	Scarlet Fever	Infectious Mono-nucleosis	Toxic Ery-thema	Others
1955	32	28	1	2	—	1	—
1956	31	26	1	1	1	—	—
1957	21	14	5	1	—	—	Mumps 1. Upper resp. tract infection 1
1958	30	24	4	—	—	2	Varicella 1
1959	17	10	3	1	—	3	—
1960	24	17	3	—	1	3	—
1961	56	41	10	1	1	2	Still's disease 1
1962	109	95	5	—	2	5	Pityriasis rosea 1. Pneumonia 1

analysis of patients referred to these departments with other diagnoses but found to have rubella. A study of these cases suggests that erroneous diagnoses arise chiefly from incomplete assessment of the clinical picture; this can result from failure to pay due attention to the prodromata of scarlet fever and measles, failure to examine the mouth for the presence of a characteristic enanthem, too-hurried appraisal of the rash, or diagnosis based solely on the appearance of the rash when first seen. We have also frequently encountered the fallacious argument that because a rash is not that of measles or scarlet fever it

must therefore be rubella. Toxic erythematous rashes of drug origin are now seen with increasing frequency and may closely simulate rubella, as may the rashes that characteristically accompany E.C.H.O. virus infections. Table III shows the number of patients in whom the pre-

TABLE II.—Patients Referred With Other Diseases Found to have Rubella

Year	Referral Diagnosis					Final Diagnosis Rubella
	Measles	Scarlet Fever	Infectious Mono-nucleosis	Toxic Ery-thema	Others	
1955	11	6	5	1	—	23
1956	5	3	—	—	P.U.O. 1	9
1957	7	4	4	—	" 2	17
1958	11	3	1	—	Meningitis 1	16
1959	1	1	—	—	—	2
1960	5	1	—	—	—	6
1961	15	4	2	—	Meningitis 1	22
1962	8	6	3	—	P.U.O. 2	19

TABLE III.—Number of Patients in Whom the Pre-admission Diagnosis Was Found to be Inaccurate

Year	No. of Patients in Series	No. Referred with Inaccurate Diagnosis	No. with Rubella
1955	55	27	51
1956	40	14	35
1957	38	24	31
1958	46	22	40
1959	19	9	12
1960	30	13	23
1961	78	37	63
1962	128	33	114

admission diagnosis was found to be inaccurate. The fact that many adults give a history of more than one attack of the disease suggests, therefore, either inaccuracy of diagnosis or the possibility of more than one aetiological agent; lifelong immunity after one attack is the normal experience.

Clinical Criteria

The clinical criteria on which we have based diagnosis are:

1. Mild prodromal symptoms with absence of coryza but with injection of the tonsillo-pharyngeal area associated with virus infection of the upper respiratory tract.

2. Cervical gland enlargement; this is practically always present, but involvement of the suboccipital nodes is variable, sometimes occurring late in the disease and occasionally failing to occur at all.

3. Suffusion of the eyes, with complaint of a sensation of grittiness. This may even occasion photophobia. We consider it a most important diagnostic sign.

4. While we agree with Wesselhoeft (1947) that there is no characteristic enanthem in this disease, petechial lesions such as were described by Forchheimer (1898) may be seen.

5. A macular type of eruption which, like measles, appears behind the ears and on the face and rapidly spreads from above downwards. As the lesions become confluent and the erythema generalized, the rash may be suggestive of scarlet fever, but the "peach bloom" appearance of the facies and absence of a scarlet-fever enanthem should prevent confusion. Differentiation from measles is based on the absence of prodromal coryzal symptoms and granular stomatitis; the fully evolved

rubella rash has nothing of the blotchy appearance of a well-developed measles eruption, while the brilliant phenomenon of "staining" so characteristic of measles is unlikely to occur in rubella unless the rash is of exceptional severity.

Table IV shows the incidence of physical signs in 114 patients with rubella seen in 1962.

TABLE IV.—Incidence of Physical Signs in 114 Patients With Rubella (1962)

Injection of tonsillo-pharyngeal area	No. of Patients
Without discomfort	80
With " " " " " "	27 } 94%
Absent	7
Glandular enlargement	
Posterior cervical and suboccipital	78
" " " " " " only	16 } 97%
Generalized	17
Absent	3
Suffusion of eyes	
Present	90
Severe with photophobia	7 } 85%
Absent	17
Palatal petechiae	
Present	19 (17%)
Absent	95

Laboratory Aids

The white blood cell count is the only laboratory investigation that has hitherto had any practical value in the diagnosis of the disease. This is characteristically leucopenic at onset, with Türk cells appearing in considerable numbers. Hynes (1940) and Hillenbrand (1956) agree as regards these features, but the former found leucocytosis at later stages, while the latter described persistence of the original picture. Further, although Hynes found that Türk cells reached a maximum on the fourth day and disappeared by the tenth day, Hillenbrand observed their persistence up to as long as nine months from the onset. In this series leucopenia was present in 63% of cases and the Paul-Bunnell test was negative in all patients with generalized lymphadenopathy.

Recent work by Plotkin *et al.* (1963) shows that identification of the virus during the first three days of the disease is feasible and that the demonstration of neutralizing antibody may provide a valuable diagnostic test.

Complications

Most patients make an uneventful recovery and may be regarded as non-infectious after the sixth day following the appearance of the rash. Transient arthralgia is the commonest complication but may be the precursor of frank arthritis. Involvement of the central nervous system occurs

more often than is generally believed (Pampiglione *et al.*, 1963). But since rubella is not a notifiable disease an accurate estimate of the incidence of encephalitis in each year proved impossible. The condition would appear to be spontaneously reversible, although Miller *et al.* (1956), reviewing 80 cases in the literature, estimated a mortality of 20% in clinically manifest encephalitis. Respiratory complications *per se* are rarely encountered; when they occur they are associated with involvement of the central nervous system. The use of corticosteroids and artificially assisted respiration may have contributed to the recent considerable fall in mortality.

Summary

Four hundred cases of rubella, or suspected rubella, admitted to two infectious diseases units from 1955–62 have been reviewed.

Even in epidemic periods, accurate diagnosis, so essential in the first 12 weeks of pregnancy, may prove difficult. Stricter attention to the clinical pattern would improve the standard of diagnosis. Confusion mostly arises with measles, scarlet fever, infectious mononucleosis, and toxic erythematous of drug origin.

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LABORATORY STUDIES ON RUBELLA AND THE RUBELLA SYNDROME

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In the past few months several reports have appeared from North America of the isolation of viral agents from cases of rubella. With one exception (Weller and Neva, 1962) the isolations were made from throat washings, and in a few instances from the blood and urine, by inoculation of monkey-kidney cell cultures prepared from the African green monkey, *Cercopithecus aethiops* (Parkman *et al.*, 1962; Sever *et al.*, 1962; Sigurdardottir *et al.*, 1963). Unlike other exanthematic viruses, such as measles, varicella, and certain strains of E.C.H.O. virus, the agents from rubella patients produced no cytopathic changes in

tissue culture, and evidence of virus multiplication could be demonstrated indirectly only by means of the interference phenomenon, a method similar to that employed by Tyrrell *et al.* (1960) in studies on the common cold. Monkey-kidney cultures inoculated with rubella material were superinfected with another virus, such as E.C.H.O. 11 or Cocksackie A 9, that was known to produce a cytopathic effect. The rubella-positive cultures resisted the challenge inoculation, in contrast to the control cultures, which were completely destroyed. McCarthy *et al.* (1963) have recently described cytopathic changes in a continuous line of rabbit-kidney cells inoculated with rubella virus.

Compared with measles, rubella or German measles is a mild disease and would be of little importance in human

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