A STUDY OF CUTANEOUS SENSITIVENESS TO SCARLATINAL TOXIN IN PREGNANCY AND THE PUERPERIUM.

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THIS paper is primarily concerned with the relation between cutaneous sensitiveness to streptococcal toxin in pregnant women and the incidence of puerperal sepsis.

The work was undertaken at the suggestion of the Streptococcal Committee of the Medical Research Council following the report of a hundred cases similarly investigated by one of us (H. B.-W.). The relationship between a positive Dick test and susceptibility to scarlet fever is now well appreciated. The close relationship between haemolytic streptococci isolated from cases of puerperal sepsis and of scarlet fever suggested that the incidence of streptococcal puerperal infection might be governed to some extent by a similar condition of sensitiveness to streptococcal toxins.

Kunz and Nobel published in 1926 the results of Dick tests carried out on 117 women before labour, and 327 within forty-eight hours of delivery. Of these 444 women, 392 (88 per cent.) gave negative reactions, and 52 (12 per cent.) positive. In the Dick-negative group 32 (8 per cent.), and in the Dick-positive group 12 (23 per cent.), experienced febrile puerperia. The febrile standard was not defined, but cases were excluded which showed a rise of temperature on one day only.

Weiss, in 1927, recorded the results of 140 Dick tests carried out during pregnancy. Of the Dick-negative women 34 per cent., and of the Dick-positive 22 per cent., were febrile during the puerperium. The febrile standard was not defined. He was of the opinion that the results were of little value, because in many cases the skin reactions were inconstant. In neither of these investigations, nor in that of Salmond and Turner, were bacteriological examinations carried out to determine specifically the incidence of *S. pyogenes* infection. It was felt that to make the investigation complete such a bacteriological examination should be made.

Method.

The Dick test was employed. A supply of standardized scarlatinal toxin prepared at the Wellcome Physiological Research Institute has been used for all tests. The Dick toxin was a filtrate of the Dochez strain grown in nutrient broth for eighteen hours at 37° C. No serum or blood had been added. The filtrate gave reactions in very sensitive people in a dilution of 1 in 6,000 and even lower, the dose used being always 0.2 c.cm. Various dilutions had been tested clinically in a number of patients suffering from scarlet fever over a long period. 1 in 1,000 was considered on the clinical results to be the most suitable dilution. Two intradermal injections—one of 0.2 c.cm. of a dilution of 1 in 1,000 of toxin, the other of heated control—were made into the skin of the ventral surface of the forearm, different arms being used for toxin and control. A positive reaction consists in the appearance within twenty-four hours of an erythematous patch measuring at least 1 cm. by 1 cm. at the site of injection, all lesser reactions being regarded as negative. In the majority of cases the test was carried out during the last four weeks of pregnancy. All cases were delivered in hospital; cases in which the reactions were ambiguous have been excluded, so that a high standard of accuracy is assured in the observations. This communication comprises the results of two separate and independent

inquiries, conducted simultaneously, at the City of London Maternity Hospital and Queen Charlotte's Hospital. The purpose of the two inquiries was identical, the results are in harmony and have therefore been published jointly. In all cases with morbid puerperia cultures were taken from the cervix whenever possible. The cervical swabs taken at Queen Charlotte's Hospital were plated out on blood agar plates; those taken at the City of London Maternity Hospital were treated by two methods: (1) the swabs were plated out on blood agar plates, and (2) were shaken up in blood broth, which was incubated for eighteen hours and then plated out on blood agar. The standard of morbidity employed was that of a rise of temperature to 100.4° F. or over, maintained for twenty-four hours, or recurring on two occasions within twenty-four hours during the first twenty-one days of the puerperium.

Results.

It has been thought best to show the main results in three tables. Table I is a summary of the 1,000 cases considered as a whole. Tables II and III represent the cases at the City of London Maternity Hospital and Queen Charlotte's Hospital taken separately.

TABLE I.—Total results of 1,000 Cases at the City of London Maternity Hospital and Queen Charlotte's Hospital.

1,000 Dick Tests			
Positive reactions 230 = 23 %		Negative reactions 770 = 77 %	
Normal puerperia 214 = 93 % 1 case infected with <i>S. pyogenes</i> .	Morbid puerperia 16 = 6.9 % 5 cases infected with <i>S. pyogenes</i> in pure culture.	Normal puerperia 732 = 95 % 1 case, a few colonies of <i>S. pyogenes</i> in mixed culture.	Morbid puerperia 38 = 4.9 % 1 case, a few colonies of <i>S. pyogenes</i> in mixed culture.

TABLE II.—The City of London Maternity Hospital.

500 Dick Tests			
Positive reactions 84 = 16.8 %		Negative reactions 416 = 83.2 %	
Normal puerperia 76 = 90.5 %	Morbid puerperia 8 = 9.5 % 4 cases infected with <i>S. pyogenes</i> in pure culture.	Normal puerperia 395 = 95 % 1 case, a few colonies of <i>S. pyogenes</i> with profuse growth of <i>B. coli</i> †	Morbid puerperia 10 = 4.8 %

* Includes 1 case of breast abscess from which *S. pyogenes* was isolated.

† Includes 3 cases of urinary infection, and 1 case of mastitis.

‡ Pyrexia just short of the morbid standard.

TABLE III.—Queen Charlotte's Hospital.

500 Dick Tests			
Positive reactions 146 = 29.2 %		Negative reactions 354 = 70.8 %	
Normal puerperia 138 = 94.5 % 1 case infected with <i>S. pyogenes</i> .*	Morbid puerperia 8 = 5.5 % 1 case infected with <i>S. pyogenes</i> in pure culture.	Normal puerperia 336 = 95 %	Morbid puerperia 18 = 5 % 1 case, a few colonies of <i>S. pyogenes</i> in mixed culture.

* This case just failed to reach the standard of morbidity. The patient's temperature was on one occasion 100.8° F., and remained for a few hours at 100° F.

† Includes one case of breast abscess.

‡ Includes three cases in which the fever was probably due to infection of the respiratory rather than the genital tract.

The results show that in a series of 230 women giving positive Dick reactions 16 (6.9 per cent.) experienced morbid puerperia, and in 5 cases a pure growth of *S. pyogenes* was isolated from the cervix; in one other case a pure growth of *S. pyogenes* was isolated from a breast abscess. In the Dick-negative group there were 770 women, and of these 38 (4.9 per cent.) experienced morbid puerperia. In this Dick-negative group, over three

times larger than the Dick-positive, 2 cases showed a few colonies of *S. pyogenes* in mixed culture. Considered purely from the point of view of the incidence of *S. pyogenes* infection the results are as follows:

In the Dick + group of women, 6 cases out of 230 = 2.6%
In the Dick - group of women, 2 cases out of 770 = 0.26%

Supplementary Investigations.

1. The Dick test was applied to 38 women at Queen Charlotte's Hospital during the puerperium—that is, either shortly after delivery or within twenty-four to thirty-six hours after the onset of fever. These were cases not included in the larger investigation. Since many of them were already febrile when the Dick test was carried out, the incidence of "morbidity" in the positive and negative groups is of no significance. Of the 38 cases, 8 gave a positive Dick reaction, and of these 5 were "morbid." Bacteriological investigation of these morbid cases showed only one infection (that is, 1 in 5) by haemolytic streptococci—a case of slight uterine sepsis. Of the 30 cases with a negative Dick reaction, 20 were febrile and were investigated bacteriologically. Three cases (that is, 1 in 6.6) showed infection by haemolytic streptococci—two being mild local infections, and the third a moderately severe case in which the fatal result was due chiefly to secondary haemorrhage.

2. The Dick test was repeated in some 26 cases at Queen Charlotte's Hospital in order to determine whether the skin reaction to streptococcal toxin changed from time to time as claimed by Weiss.

15 cases were tested before labour and once during the puerperium.

4 cases were tested before labour and twice during the puerperium.

7 cases were tested twice during the puerperium.

Ten of the patients tested were Dick-positive, 16 of them Dick-negative. In only one case was there a different reaction on re-testing—a positive before labour changing to a negative after labour in a patient whose puerperium was afebrile.

Conclusions.

1. There is a suggestion that women with positive Dick reactions show an increased susceptibility to puerperal morbidity. In this series the morbidity in the Dick-positive was 41 per cent. greater than in the Dick-negative group.

2. The Dick-negative group was three times as large as the Dick-positive, but the actual number of cases infected with *S. pyogenes* was greater in the positive group.

3. Even if the pure cultures of *S. pyogenes* in the positive group be considered to be on an equal footing with the mixed cultures of *S. pyogenes* occurring in the negative group, the incidence of *S. pyogenes* infection in the puerperium was ten times greater in the Dick-positive group (6 cases out of 230) than in the Dick-negative group (2 cases out of 770).

4. It is suggested that skin sensitiveness to scarlatinal toxin may indicate a special liability to streptococcal infection, but definite conclusions cannot safely be drawn from a series including so small a number of cases of *S. pyogenes* infection. It would have been necessary to extend the inquiry to a group of not less than 10,000 women to obtain anything like conclusive evidence on this point.

5. In view of the comparative rarity of streptococcal infection (0.8 per cent.) which is demonstrated by the present investigation, there would seem to be no case for the active immunization of all expectant mothers, nor even of all who are Dick-positive. Until data are available which show more conclusively whether there is a close correlation between Dick-sensitiveness and streptococcal infection in the puerperium, it is suggested that Dick testing should be confined to women who have passed through complicated labours, and that the positive reactors among these might be immunized passively by the injection of streptococcal antitoxic serum.

We wish to express our thanks to the committees of management and the staffs of Queen Charlotte's Hospital and the City of London Maternity Hospital for permission to utilize their cases. Our thanks are also due to the resident medical officers of these hospitals

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THE FREQUENCY OF STREPTOCOCCUS PYOGENES INFECTION IN PUERPERAL FEVER.

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PUBLISHED reports from all over the world have made it clear that the most common infecting agent in severe puerperal fever is *Streptococcus pyogenes*. It has been commonly assumed that this microbe is responsible also for most of the less severe infections of the puerperium. Some recent investigations, however, have thrown doubt upon that assumption. White (1927) in Melbourne found only one *S. pyogenes* infection out of a series of 25 cases of so-called "sapræmia" bacteriologically examined; Lucy Bryce (1928), also in Melbourne, reported 6 cases out of 50; and more recently Armstrong and Burt-White reported 8 such infections in a series of 34 mildly febrile cases.

The Dick test inquiry reported in the preceding article by Burt-White, Colebrook, and others, afforded a suitable opportunity for obtaining further data about the incidence of streptococcal infections. For a period of nine months practically every case at Queen Charlotte's Hospital which developed a temperature of 100° F. or more at any time after the first fifteen hours of the puerperium has been investigated bacteriologically—that is, by culture (on blood agar plates) from the cervix uteri, and in some cases also from the blood and urine. The cases so examined include all those classed as "morbid" in the Dick test inquiry.

S. pyogenes was identified by the following characters: its colonies, after twenty-four hours' incubation on horse or human blood agar (3 to 5 per cent.), were surrounded by a zone of 1 to 2 millimetres in which the red corpuscles were destroyed and the haemoglobin decolorized. (Later this zone increased somewhat in width.) These colonies were always round, slightly convex, semi-transparent at their periphery, becoming rather more opaque at the centre; their surface was usually matt, they did not adhere to the medium, and they were of soft consistency, allowing the platinum loop to sink into them. The stained cocci from such surface colonies were round. In a word, they correspond to the beta type of Brown (1919). The total figures obtained were as follows:

Deliveries	...	...	...	...	...	1,626
Febrile (all grades except those limited to the fifteen hours following labour)	...	...	...	...	...	134
Infections by <i>S. pyogenes</i>	...	...	...	...	...	10

It appears, therefore, that infection by *S. pyogenes* is a comparatively infrequent cause of the minor febrile disturbances of the puerperium. Much more commonly these were associated with infection by *B. coli*, diphtheroid bacilli (minute colonies on blood agar), non-haemolytic streptococci, and various unclassified Gram-negative organisms. Whether the presence of these organisms indicates actual infection of the tissues or not, has not been determined.

One or two other points of interest may be noted. First, the cases infected with *S. pyogenes* were not all of a clinically severe type. Only one died (from secondary

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