THE WEIL-FELIX REACTION IN TYPHUS FEVER.

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(With one Chart.)

The Weil-Felix reaction derives its name from the interesting phenomenon discovered by Weil and Felix in 1916 that the organism *Bacillus proteus* X. 19 is agglutinated by the serum of practically all cases of typhus fever after the first week of illness. The diagnostic value and specificity of the test have been confirmed by numerous workers (Wolbach, Todd and Palfrey, G. Stuart, etc.), and, while it has been shown (Kapsenberg) that cases of paratyphoid fever, smallpox and scarlet fever may give a positive reaction in dilutions of the serum not exceeding 1 : 50, agglutination of the organism by the serum of a suspected case in a dilution of 1 : 100 may be regarded as diagnostic of typhus (Reynolds). The test as performed is analogous to the Widal reaction in enteric fever, with this difference that *B. proteus* X. 19 has not, so far as present knowledge goes, any etiological relationship to typhus. This organism, distinguishable from other members of the Proteus family only by its particular fermentative reactions, was first isolated from the urine of a case of typhus (Weil and Felix), and has since been recovered, although infrequently (*vide* Schürer and Wolff), from the blood, as well as from the urine, of patients suffering from typhus. Its infrequent isolation, however, from either the urine or blood of such cases minimises its claims to be regarded as the causal organism. Further, the intimate association of the *Rickettsia prowazeki* with the transmission of the disease from lice to man has been conclusively proved by its presence, not only in the intestines of lice allowed to feed on infected persons (Arkwright and Bacot), but also in the blood-vessels of the skin, kidney, liver, etc., of typhus patients (Wolbach, Todd and Palfrey). While, therefore, it is difficult to explain the occasional presence of *B. proteus* X. 19 in the urine and blood, the Weil-Felix reaction must be regarded not as a specific antigen-antibody reaction, but as a heterologous one, perhaps similar to the Wassermann reaction in syphilis.

The value of the reaction has become enhanced in recent years since unfamiliarity with typhus, due to the rare occurrence of the disease in this country, has increased the difficulty of diagnosis from the clinical phenomena alone. The tendency, too, for the infection to manifest itself in an atypical form during inter-epidemic periods adds further to the uncertainty of diagnosis until the Weil-Felix reaction has shown whether or not the case is one of typhus. For example, a definite diagnosis of the primary case in the present outbreak could not be made until the result of the Weil-Felix reaction (positive

1 : 1000) was ascertained. In 36 out of 87 groups of the disease occurring in Glasgow since 1901 the primary case was not diagnosed as typhus. It is obvious, therefore, that the Weil-Felix reaction is even more essential for the diagnosis of typhus than is the Widal test for enteric fever, since the recovery of the causative organism in typhus is beyond the scope of the ordinary laboratory.

PERFORMANCE OF THE TEST.

In a small outbreak of typhus in Glasgow (Davidson and Cruickshank) 7 of the 8 cases were members of one family, whose ages ranged from 10 to 27 years, the eighth case being a woman of 50 years. The primary case was admitted on the eleventh day of his illness, and the others, who were presumably infected from this case, on the first to fifth day of illness. The Weil-Felix reaction was performed daily with each patient's serum from the day of admission till the crisis, thereafter every second or third day for two to four weeks, and then at longer intervals till the reaction became negative. It was thus possible to secure complete curves of the degree of positivity of the Weil-Felix reaction in each patient throughout his or her illness (as shown by the varying dilutions of the serum which agglutinated the organism), and, in addition, to determine (*a*) how early in the disease the reaction became positive, and (*b*) how long after convalescence it persisted. Such a systematic investigation has not apparently been hitherto undertaken, and the value of the data so obtained is obvious as an aid to tracing missed or convalescent cases of typhus. The cerebro-spinal fluid of six of the patients was also tested for the presence of agglutinins during the first week of illness and again at or near the crisis.

Method. An unheated emulsion in normal saline of a twenty-four hours' culture on an agar slope of *B. proteus* X. 19[1] was used as the bacterial antigen, to which was added the patient's serum in dilutions varying from 1 : 25 to 1 : 5000. The tubes containing bacterial emulsion, *plus* patient's serum, were then immersed in the water bath for two hours at 56° C., and readings made after they had stood at room temperature for twenty minutes. The standard of agglutination readings was that of the Oxford Standard Laboratories. Subcultures of the organism were made from day to day and always a fresh *unheated* emulsion was used, since Sachs has shown that heating the organism at 56° C. destroys its agglutinability (although a suitable emulsion is obtained by heating at 80° C. and preserving with phenol). That there could not have been any spontaneous falling off in the agglutinability of the organism is proved by the fact that while the serum-titre of the primary case was falling (in convalescence), the titres of the sera of the other patients who were still in the early stage of the infection, were steadily increasing to higher dilutions. Wilson has shown that the agglutinins in the patient's serum are thermolabile

[1] The culture of *B. proteus* X. 19 was supplied by Dr R. M. Buchanan of the Public Health Laboratory, Glasgow.

to the extent that they are destroyed by heating at 65° C. for half-an-hour; in the present work no appreciable change in the agglutinating power of the serum was noted after the serum had been heated at 56° C. for half-an-hour, one hour, and two hours respectively. Stuart has advocated heating of the serum at 56° C. for half-an-hour to inhibit zone phenomena.

Results.

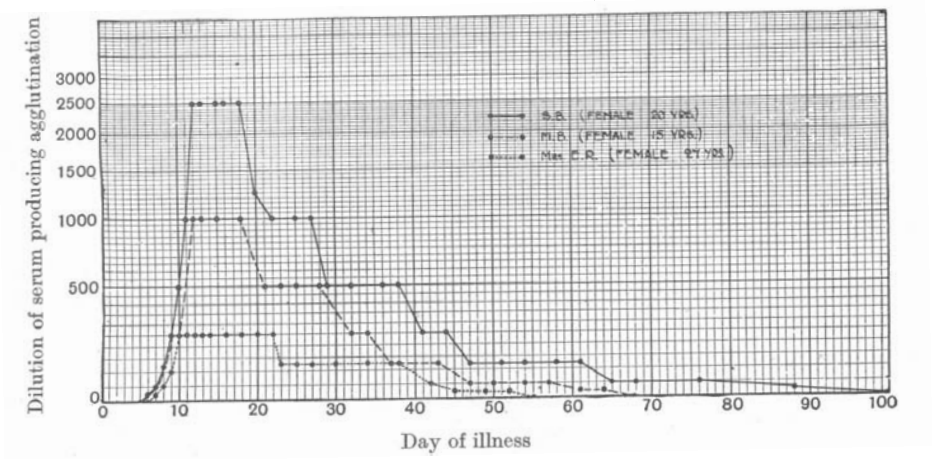
The earliest day of illness on which agglutinins were demonstrated in the blood was the fifth, when a 1 : 25 dilution of the serum of M. B. (F., 15 years) agglutinated the emulsion of *B. proteus* X. 19. The serum of other cases agglutinated the organism in a similar dilution, or in 1 : 50 on the sixth and seventh days of the fever. The agglutinating power of the serum increased rapidly on each succeeding day until the maximum dilution at which the serum agglutinated the organism was reached. This varied from 1 : 250 (Mrs E. R., 27 years, and J. B., 13 years) to 1 : 2500 (G. B., 25 years, and S. B., 20 years) except in the case of W. B. (10 years), whose serum did not produce agglutination in a dilution beyond 1 : 50 at any time. The fact that the serum-titre of the youngest patient (W. B., 10 years), whose infection was the mildest, did not exceed 1 : 50, whereas that of the older and more severely ill cases was 1 : 1000 to 1 : 2500, seemed to indicate some correlation between the degree of severity of the illness and the formation of agglutinins in the blood. That age was not the sole factor was shown when the serum of M. B. (15 years), who was very acutely ill, reached a maximum agglutinating dilution of 1 : 1000, while that of MY. B. (18 years), whose infection was milder, only reached 1 : 500. On the other hand, the serum of Mrs E. R., who for a week (14th to 21st day of illness) was in an extremely ill state, did not agglutinate the organism in a dilution beyond 1 : 250. This patient was probably too ill to react to the infection by a greater formation of antibodies.

In each case the maximum agglutinating dilution was reached two to three days before crisis—tenth to twelfth day of illness—and was maintained for four to seven days after the crisis. Thereafter it fell, at first rapidly and then more slowly, until the reaction became negative at a period varying from six weeks to three months from the onset of the illness, according as the titre was a low or a high one. Doubtless, in cases where the titre of the serum is higher than were those of the present series, the period during which a positive reaction may be expected will be extended, but obviously the comparatively early stage at which agglutinins disappear from the blood of infected persons—even in acutely ill patients (see chart, Mrs E. R.)—increases the difficulty of a retrospective diagnosis in a missed or suspected case. By contrast, the Widal reaction in enteric fever may remain positive, although in low dilutions, for months or years after infection: even in vaccinated cases positive Widal reactions in dilutions of the serum varying from 1 : 200 to 1 : 800 may be obtained seven to fourteen months after inoculation (Martin and Upjohn).

The accompanying chart relating to three representative cases shows the

rapid rise in the agglutinating power of the serum and the more gradual decline until the reaction becomes negative.

Controls. No agglutination was obtained when the sera from four cases of enteric fever, four of paratyphoid B., and six of scarlet fever were tested against *B. proteus* X. 19 in dilutions commencing from 1 : 25. Conversely, the sera of six patients affected with typhus failed to agglutinate Dreyer's standardised T.A. and B. emulsions, while two patients gave negative reactions when the serum of each was tested with three strains of *B. typhosus* and five coliform strains (the highest concentration of serum tested was 1 : 25): three of these coliform organisms had been isolated from the urines of three of the patients. Mathieson and Leete reported positive Widal reactions in three of



This chart represents graphically the Weil-Felix reaction in three of the patients throughout their illness and convalescence.

their cases (T. 1 : 100, T.A.B. each 1 : 200, and T. 1 : 400 respectively). Other observers (Patterson, Fairley, etc.), have obtained positive Widal tests—even in high dilutions—with the serum of typhus patients, and Wilson originally wrote: "From a wide experience of the test in many outbreaks of typhus, I can state that in certain of these the Widal test is uniformly negative, whilst in others it is in a considerable number of cases as markedly positive as if the patients were suffering from enteric fever." The presence in the blood of agglutinins to coliform strains isolated from the faeces and urine of typhus patients has also been demonstrated (Wilson).

Cerebro-spinal fluid. In only two cases (S. B., 20 years, and M. B., 15 years) were agglutinins demonstrable in high concentrations of the fluid at or near crisis. The cerebro-spinal fluid of M. B. agglutinated *B. proteus* X. 19 in a dilution of 1 : 5 at the time when the agglutinating power of the blood serum was at its maximum (1 : 1000), and similarly a 1 : 10 dilution of the cerebro-spinal fluid of S. B. agglutinated the organism when the serum-titre was 1 : 2500.

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Wassermann Reaction.

The Wassermann reaction obtained before the crisis—tenth to twelfth day of illness—was positive[1] in four out of six cases. Negative reactions were obtained with the serum of J. B. (13 years), whose infection was of a milder nature, and with that of Mrs McG. (50 years), whose blood was tested on the sixth and eighth days of her illness. Mrs E. R. and S. B.—the two patients most ill—still gave positive reactions on the twenty-third day of infection, while the others reacted negatively. A week later all cases gave negative reactions. In 1921, Bauer found that of 50 patients whose blood was tested for the Wassermann reaction before crisis 46 were positive, while, when tested in convalescence, 20 out of 21 gave negative reactions. The findings in the present series corroborate his statement that the Wassermann reaction in typhus is almost always positive at or near crisis and becomes negative again in convalescence.

Conclusions and Summary.

(1) Statistical evidence cannot be deduced from such a small series of cases, but it would seem that the extent to which agglutinins for *B. proteus* X. 19 (Weil-Felix) were formed in the blood varied directly as the severity of the illness, since with the older and more ill patients a much higher dilution of serum agglutinated the organism at or near crisis than was the case with the younger patients, who were less acutely ill. An exception to this rule was met with in one case (Mrs E. R.), whose serum did not agglutinate the organism in a dilution beyond 1 : 250, although she was the most severely ill of all the patients. It is possible that failure of agglutinin-formation resembles the absence of leucocytosis in the severely ill case of pneumonia and may be regarded as a bad prognostic feature.

(2) A positive Weil-Felix reaction was not obtained before the fifth day of illness, nor in any case before the characteristic rash appeared, so that the reaction is of little value as a factor in the early diagnosis of typhus. Later, a reaction in which a dilution of the serum of 1 : 50 agglutinates the organism may be regarded as diagnostic of typhus.

(3) The Weil-Felix reaction remained positive for the longest period in those cases whose serum agglutinated in highest dilution, and in these patients a positive reaction (1 : 25–1 : 50) was still present nine to twelve weeks after infection, whereas in the milder cases, and in Mrs E. R., the reaction became negative in six to eight weeks from the onset of illness.

(4) In view of this heterologous reaction in typhus, it is interesting to record that the Wassermann reaction obtained before crisis was positive in four out of six cases. It was still positive in two of the most severely ill patients a week after crisis, but was negative in all cases a week later.

[1] The tests were carried out in the City Public Health Laboratory, Glasgow. Harrison's method was used, and the fixation of five M.H.D.'s of complement was reported as a positive (++) reaction.

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