A disadvantage of the reaction is that in an ordinary severe case by the seventh day, the earliest day on which one can guarantee a definite result, the diagnosis, clinically, is usually beyond doubt. This, however, does not apply in the milder form of the disease, where the diagnosis is often in doubt until about the fifteenth day, when the temperature drops suddenly.

Our thanks are due to Captain W. Rees-Thomas, R.A.M.C. (T.C.), for much valuable assistance, and to Captain D. Craig, R.A.M.C. (T.C.), who was in charge of the isolation hospital, for supplying us with most of the specimens and for allowing us free access at all times to his wards.

STUDIES ON THE
WEIL-FELIX SEROLOGICAL TEST
FOR THE LABORATORY DIAGNOSIS OF TYPHUS FEVER.
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TOWARDS the close of 1918 and the beginning of 1919, during the typhus season in Syria, I had an opportunity of carrying out a number of blood tests on cases of acute typhus, from the point of view of the Weil-Felix reaction recently described in connexion with this disease.¹ The reaction, be it recalled, is an expression of the power often possessed and developed during the disease by the blood serum of the typhus patient, of specifically agglutinating in vitro a bacterial emulsion of *B. proteus* X 19. Although the studies with which this paper deals make no pretence at being exhaustive—which they could scarcely be, considering the “field conditions” under which they were carried out—still, in the confirmation which they afford of the constancy of the reaction in the disease, a short account of them may prove instructive. The contribution is merely a pioneer one.

Clinical Material and Technique.

Forty-seven blood tests were performed in all, on some 14 cases (British, Indian, and Turkish prisoners of war) of the disease, the tests ranging from the fourth to the thirty-fourth day of illness, and consequently covering the various stages of the disease from onset to convalescence.

To Captain William Forsyth, R.A.M.C., and to Captain K. B. Dickson, R.A.M.C., under whose clinical care these cases were, my best thanks are due for placing them at my disposal for the purpose of this investigation.

Blood from the patient's thumb was collected in a Wright's blood tube, and on arrival at the laboratory was centrifuged to separate off the serum. The agglutination titre of the latter was then determined towards a 10-12 thousand bacterial emulsion of *B. proteus* X 19 in saline phenolated to 0.5 per cent. The slide method of macroscopic agglutination associated with the names of Alcock² and Garrow³ was employed, the results being read off after three minutes' rotation of the slide in the agglutinator-box.

Experimental Findings.

The table here given briefly summarises the main features of the cases, and the results of the blood tests performed.

The table (columns 5 and 6) shows that these cases all, with the exception of Case 3, gave a markedly positive reaction from the first days of the disease, and that the strength of the reaction varied from day to day. Some idea of the nature of this variation is revealed by the accompanying diagram, which is a graphical representation of the findings for Cases 1 and 2.

The curves show that the Weil-Felix reaction in typhus fever steadily increases during the first fortnight to attain its maximum about the twelfth to fourteenth day of the disease (the period when, in the uncomplicated case, the temperature, as a rule, falls by crisis), to decrease rapidly thereafter during the period of convalescence. This finding indicates to what extent, other things being equal, the Weil-Felix reaction may render conspicuous service to the physician. It points to the

conclusion that in an early case of doubtful pyrexia, which shows a positive Weil-Felix reaction steadily rising in the 24 hours, there is strong presumptive evidence of typhus fever.

No. of case and name.	Nationality.	Date in 1919 of blood specimen.	Rash.	Day of illness (patient's statement).	Result of agglutination test, for following dilutions of patient's serum. (Saline control: negative.)						Date patient's temp. fell to normal.
					1/2	1/10	1/50	1/100	1/200	1/300	
1. S.	British.	1/1	Present	7	VM	VM	VM	D	-	-	5/1
		5/1		12	"	"	"	VM	D	-	
		8/1		15	"	"	"	"	"	-	
		12/1		19	"	"	"	D	F	-	
		17/1		24	"	"	"	D	-	-	
		21/1		28	"	"	"	F	-	-	
		27/1		34	"	"	"	-	-	-	
2. R.	"	5/1	"	4	"	"	"	-	-	-	12/1
		8/1		7	"	VM	VM	D	F	-	
		10/1		9	"	"	"	VM	D	-	
		12/1		11	"	"	"	"	"	F	
		17/1		16	"	"	"	"	F	-	
		19/1		18	"	"	"	D	"	-	
		21/1		20	"	"	"	F	-	-	
3. H.	"	8/1	"	7	-	-	-	-	-	-	17/1
		10/1		9	-	-	-	-	-	-	
		12/1		11	-	-	-	-	-	-	
		17/1		16	VM	-	-	-	-	-	
		19/1		18	"	F	-	-	-	-	
		22/1		21	D	-	-	-	-	-	
		27/1		26	"	-	-	-	-	-	
4. Capt B.	"	9/1	Absent. Present	4	"	-	-	-	-	-	19/1
		10/1		5	VM	D	-	-	-	-	
		12/1		8	"	VM	-	-	-	-	
5. S.R.	Turkish P. of W.	10/1	"	5	"	-	-	-	-	-	19/1
		15/1		10	"	VM	F	-	-	-	
		23/1		14	"	"	-	-	-	-	
6. M.A.	"	10/1	Absent. Present	4	"	"	-	-	-	-	19/1
		15/1		9	"	"	VM	VM	-	-	
		23/1		17	"	"	D	-	-	-	
7. A.S.	"	10/1	Absent. Present	4	"	"	-	-	-	-	21/1
		15/1		9	"	"	VM	VM	-	-	
		23/1		17	"	"	D	-	-	-	
8. M.	British.	23/1	"	5	"	D	-	-	-	-	15/1
		25/1		7	"	VM	F	-	-	-	
		27/1		9	"	"	D	-	-	-	
9. O.M. A.	Turkish P. of W.	10/1	"	10	"	"	VM	D	F	-	21/1
		23/1		23	"	"	F	-	-	-	
10. Y.S.	"	10/1	Fading.	12	"	"	D	F	-	-	22/1
		23/1		25	"	"	D	-	-	-	
11. M.H.	"	10/1	Present	5	"	VM	F	-	-	-	11/1
		23/1		18	"	"	-	-	-	-	
12. K.S.	Indian.	11/1	"	9	"	"	VM	D	-	-	
13. R.R.	"	12/1	"	9	"	"	D	-	-	-	
14. Y.M.	Turkish P. of W.	15/1	Present 4 days.	6	"	VM	D	-	-	-	

¹ E. Weil and A. Felix: Wien. Klin. Woch., xxi. (No. 2), 1916, 33-35.
² Broughton Alcock: Journ. R.A.M.C., xxx., 1918, 424-431.
³ R. P. Garrow: THE LANCET, i., 1917, 262; Journ. R.A.M.C., xxviii., 1917, 566-572.

VM = Agglutination very marked. D = Agglutination distinct to naked eye. F = Agglutination feeble, requiring hand-lens to be certain. - = Agglutination negative.

Case 3 appeared to us at first an exception (see tests of Jan. 8th, 10th, and 12th), there being no doubt clinically as to the diagnosis of typhus. This man's Weil-Felix reaction was persistently negative throughout the first fortnight, to become positive about the sixteenth day of the disease, when it was observed for the first time, his blood having then acquired the power to agglutinate markedly *B. proteus* X 19 in a serum dilution of 1/2, but not beyond. On the sixteenth day his temperature fell by crisis. A blood test 48 hours later revealed that the titre of agglutination, although still low, had increased slightly, being well marked in the 1/2 dilution and feebly so in the 1/10 dilution. Thereafter in his case, as in the others, this feebly positive Weil-Felix reaction, which might well have been missed on the method employed had it not been persistently studied in very low dilutions, gradually fell off, its maximum having been reached.

Of the 14 cases, then, of typhus fever tested by us 13 showed well-marked Weil-Felix reactions, and one gave such a feeble reaction that it might well have passed unperceived and been returned as negative.

Conclusion.

The significance of positive Weil-Felix reactions, other than the practical one that they may be utilised as a laboratory method for the diagnosis of typhus, is unknown.⁴ As to that of such feebly positive reactions as the one above described—for no truly negative Weil-Felix reaction has been met with in any case of typhus examined by me—it may be that such reactions are related to the curious phenomenon, recently described by Nicolle and Lebailly,⁵ of “inapparent infection.” In the latter phenomenon, observed so far only in laboratory animals in connexion with experimental typhus, a guinea-pig occasionally shows no temperature reaction following inoculation with the virus of typhus, and yet its blood, at the time when the control animals show well-marked fever, is found to be virulent, especially for the African monkey. Rats, again, do not ordinarily react, even by an elevation of temperature, to the virus of typhus, but their blood is nevertheless virulent about the twelfth day.

These, then, are some, at least, of the problems connected with this interesting disease which it is for future investigation to solve.

OSTEITIS FIBROSA.

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THE condition known as osteitis fibrosa is now recognised to be a good deal commoner than was at one time supposed, but even at present some obscurity attaches to it, partly on account of the very mixed nomenclature under which it has been described and partly because it is still in many cases confused with, and described in conjunction with, several other entirely different diseases occurring in bone.

The fact that osteitis fibrosa frequently leads to cyst formation, and that the consequences of such cyst formation in bone are often the patient's reason for seeking advice, has led to a tendency to presume osteitis fibrosa as the cause of the cyst formation in such cases, often on inadequate evidence, and in many of the published cases the diagnosis is left as “cyst in bone” without any detail as to the underlying condition. That many such cysts in bone depend upon a cystic degeneration occurring in the course of osteitis fibrosa is undoubted, but, on the other hand, there is good reason to think that some of the other conditions leading to cyst formation—e.g., extreme degeneration of a myeloma, the so-called blood cyst, callus cyst, &c.—are less rare than some writers would have us believe. A further difficulty occurs in the fact that opinion appears to be still divided as to whether osteitis fibrosa, as it occurs in a single bone, and von Recklinghausen's multiple fibro-cystic disease of the bones are or are not identical conditions. The rarity of the latter and the lack of sufficiently long after-histories of the former make it difficult to hazard an opinion, but such evidence as there is would rather lead one to the belief that

the two conditions are unconnected, excepting in so far as in both there occurs a localised or generalised replacement of the bone marrow by a fibroid tissue. I can find no case in the literature of the appearance of osteitis fibrosa in other bones after its operative treatment in any one bone. A case reported by V. P. Gibney of a cystic condition in the femur of a boy of 12, followed a year later by an apparently similar condition in the fibula of the same side, is anomalous in that both were operated on, and the pathological report on the condition in the fibula was “a chondroma with extensive calcareous areas and some cellular connective tissue,” while in the case of the femur opinion was divided between osteitis fibrosa and “osteo-chondro-fibroma.” Further, von Recklinghausen's disease occurs, as a rule, fairly late in life, while osteitis fibrosa is essentially a lesion of the epiphyseal period. In spite of the above-mentioned confusion sufficient data now exist to enable a fairly definite clinical and pathological picture of the condition known as osteitis fibrosa to be built up, and the satisfactory results that have followed its treatment by comparatively simple means make it desirable that it should be more often recognised in its earlier stages, and before its extension and complications have led to the production of considerable deformity.

Etiology.

Many theories have been advanced to account for this condition since Virchow's original description of two cases which he regarded as the result of degeneration occurring in a chondroma. At the present time opinion is fairly evenly divided between the views that (1) it represents a metaplastic transformation of the bone marrow into a fibroid tissue, and (2) that it is the result of a chronic inflammation of unknown origin occurring in the endosteum. Whatever view is held as to its exact pathology, certain predisposing factors are fairly constantly present.

Trauma.—There is no definite evidence that trauma is of much importance as an ætiological factor, though in many cases the patient first has his attention drawn to the condition by the disproportionate results of comparatively slight accidents. It is by no means uncommon for a pathological fracture following some slight injury to be the first important symptom, and only on careful questioning are previous symptoms suggesting the condition brought to light. Bloodgood denies that trauma is in any sense a causative factor, but the predilection which osteitis fibrosa shows for the juxta-epiphyseal region of the bones, together with the importance of slight injuries in this region as a predisposing factor in other bone diseases, suggest that frequency of a history of trauma may have considerable significance.

The Influence of Sex and Age on the Condition.

Sex does not seem to influence the appearance of the condition. Age, on the other hand, has an important bearing, the great majority of the cases occurring before the twentieth year and the commonest age being about 12. The case from which the accompanying radiogram was taken is exceptional in that her age on presenting herself was 25, and in spite of the most careful questioning no suggestion of anything abnormal could be obtained in her history earlier than two years previously. Silver reports 97 cases, of which 75 occurred before the twentieth year and 22 after. These figures, however, are of little value, as many of the cases were undoubtedly cases of cysts occurring in sarcomata, chondromata, &c., and in many of the others there was no proof that the pathology of the cyst present was connected with osteitis fibrosa. In Bloodgood's 69 cases five only were over 20 years at the time of onset; but here again the pathology seems uncertain, especially in the group of cases in which a cyst only, with no lining membrane, and therefore no evidence of origin, was found. A. Tietze published a series of 24 cases, which appear to have more value in this respect in that they represent a group of definite cases of osteitis fibrosa. In these 24 cases, 20 patients were under 20 years of age and two were between 20 and 30; two were over 30 at the time when they came under observation, and in these it is noted as probable that the disease had already been present for a long time.

Bone Affected.

Three of the long bones of the skeleton seem particularly liable to this condition—namely, the femur, the humerus, and the tibia. Muller gives 38 per cent. in the femur, 22 per cent. in tibia, and 16 per cent. humerus. Bloodgood

⁴ C. Craig and H. Fairley (THE LANCET, Sept. 28th, 1918, 386) view the Weil-Felix phenomenon in the light of a group agglutination, the virus of typhus being probably an organism allied to *B. proteus* X 19, but resistant to cultivation on ordinary media.

⁵ Ch. Nicolle and Ch. Lebailly: Comptes rendus, clxviii., 1919, 800.