instil into the patient's mind certain principles of mental hygiene which he had previously ignored. The importance of the constitutional factor must not be forgotten; but this should only emphasize the need for the patient to live within the limits of his capacity. There is no evidence that convulsion therapy has any power to prevent the recurrence of depression in the future. Experience over many years has, however, taught us that mental hygiene, sensibly applied, can greatly influence the probability of relapse.

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ABNORMAL AGGLUTINATION REACTIONS OF A STRAIN OF *LEPTOSPIRA ICTEROHAEMORRHAGIAE*

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Proof of the diagnosis of Weil's disease (spirochaetal jaundice) depends in most instances on serological investigation. It is often impossible to differentiate this condition, on clinical grounds alone, from infective hepatitis (catarrhal jaundice), and only on rare occasions are leptospira seen in the blood or isolated by culture or guinea-pig inoculation during the first few days of the disease. Most commonly, Weil's disease is suspected because the patient, by vocation or chance, is brought into contact with rats (e.g., working in sewers, damp mines, fish-markets; immersion in canals or stagnant pools). Confirmation is obtained from the blood count, which in Weil's disease shows a polymorphonuclear leucocytosis; and proof is furnished by the presence in the serum of increasing amounts of antibody to *Leptospira icterohaemorrhagiae*.

The agglutination test is generally used to detect the presence of antibodies, and the specificity of the reaction has been well established, although care is needed in the choice of strain, preparation of antigenic suspension, and interpretation of results (Brown and Broom, 1939). In our case, for routine tests we chose, after a considerable amount of experimental work, a strain of *L. icterohaemorrhagiae* (Jackson) which we isolated in 1934 from a London sewer-worker suffering from Weil's disease. Cultures of this strain, grown in Fletcher's rabbit-serum-broth medium and formalinized to 0.2%, were used for eight years. This strain proved satisfactory throughout that period as judged by the correlation between the agglutination results and the clinical histories, blood pictures, and (in positive cases) the occasional isolation of leptospira from the blood or urine of patients.

Recent Abnormal Reactions

During the autumn of 1942, however, the sera of 34 cases of jaundice admitted to the Cambridge Hospital, Aldershot, were found to agglutinate this strain of *L. icterohaemorrhagiae* although there was nothing in the history of these patients to suggest that they were suffering from Weil's disease. In addition, differential blood counts were either normal or showed a relative mononuclear increase, as occurs in infective hepatitis, instead of the polymorphonuclear leucocytosis characteristic of leptospirosis. Nevertheless, these sera produced a true agglutination of *L. icterohaemorrhagiae* (Jackson). The agglutinated clumps, examined by dark-field illumination with a 1/12-in. objective, proved to consist of leptospira, thus

differing from the false agglutination referred to by Brown and Broom (1939). During the course of the disease in these patients the agglutination titre of the serum rose to a limited extent (titres of 1/300 were not unusual) and then disappeared completely in a few weeks. In true Weil's disease the titre commonly reaches 1/10,000 to 1/30,000, and remains demonstrable, though at a lower level, for years after recovery.

The occurrence of a positive agglutination and the rise in titre during the disease suggested the possibility of atypical Weil's disease. Centrifuged deposits from the urine of patients between the fifteenth and twenty-third days of disease were examined microscopically by dark-field illumination, and were scarified into guinea-pigs by Lieut.-Col. N. T. Whitehead, R.A.M.C. All precautions were of course taken to examine as fresh urine as possible; and alkalis were administered to the patients to render the urine slightly alkaline. Blood taken from patients during the first ten days of the disease was also inoculated into guinea-pigs. In no case were leptospira seen and no guinea-pig became infected.

Protection Tests

The serum from cases of Weil's disease will normally protect guinea-pigs against infection by a virulent strain of leptospira. Pooled serum from six of the Aldershot cases was therefore injected intraperitoneally into guinea-pigs, each animal receiving a single dose of 5 c.cm., 2.5 c.cm., or 1 c.cm. The same doses of known anti-leptospira serum were given to another series of guinea-pigs. All the animals, and also controls which had received no serum, were inoculated with 0.5 c.cm. of a virulent culture of *L. icterohaemorrhagiae* (W.P.R.L. strain). The temperature of each animal was taken and recorded daily.

The results of this experiment were unusually clear-cut for a protection test. The anti-leptospira serum protected all the animals, none of which showed even a rise of temperature. The control guinea-pigs and all those which had received the pooled Aldershot serum showed the accustomed signs of leptospirosis in guinea-pigs—namely, temperatures mounting to 106° F. followed by a sudden fall to subnormal, and terminated by death between the fifth and seventh days. Post mortem the appearances were typical, and leptospira were seen in microscopical preparations from the livers.

Further Tests

Additional serological tests were carried out with other strains of *L. icterohaemorrhagiae*—namely, one human strain (Coppard) and two rat strains (Wild Rat and W.P.R.L.), all of which agglutinate well with anti-leptospira sera. The sera under investigation failed to agglutinate these strains. In addition, the adhesion test described by Brown and Davis (1927) was applied to these sera. The same strain (Jackson) which gave the spurious original agglutination results was used, but as a living, not a formalinized, culture. The adhesion test was consistently negative with these sera. These serological tests were carried out in duplicate, independently, in London and Aldershot, and only insignificant quantitative differences were obtained by the two workers.

It is apparent, therefore, that formalinized suspensions of this particular strain have become unduly sensitive to sera of certain cases of jaundice other than Weil's disease. The effect is not caused by the presence of bile in the serum reducing interfacial tension, because serum from a number of cases, including twelve of arspenamine jaundice, produced no agglutination.

It seemed possible, therefore, that the result might be due to an altered protein ratio of the serum. We had intended to carry out protein-fractionation of all sera, but unfortunately pressure of other work rendered this impossible. However, to test this point with serum the protein ratio of which was known to be altered, blood from 25 patients suffering from various diseases which produce a high red-cell sedimentation rate was kindly supplied to us by Dr. J. M. Alston. Only one serum agglutinated *L. icterohaemorrhagiae* (Jackson); the others were all negative. The positive serum was from a child with a rheumatic condition; but after a few days in hospital he was removed by his parents and lost sight of.

There was no suggestion, therefore, that the protein changes which produce high E.S.R. are responsible for the agglutination.

Abnormal Behaviour of *L. canicola*

At this stage in the investigation a paper by Das Gupta (1942) appeared in which he stated that a particular strain of *L. canicola* had recently become agglutinable by normal human serum. Das Gupta found that this non-specific agglutination did not take place if the serum were heated to 56° C. for half an hour before use.

This abnormality differs from the one we have described because the suspensions of *L. canicola* were agglutinated by normal serum. However, we retested several samples of the sera under investigation against the Jackson strain after they had been heated. The agglutination titres were reduced but not abolished. This reduction of titre is not due to destruction of complement, because sera which had been held at room temperature for periods up to six weeks still produced agglutination, and after that time no complement could have been present.

Reversion of *L. icterohaemorrhagiae* to Normal

The leptospira suspensions with which these investigations were carried out were prepared from serial subcultures of the strain, and the aberrant agglutinations occurred with the different lots in use from Sept. to Nov., 1942. Later in November it was realized that no further sera which were without effect on the other strains were agglutinating the Jackson strain. Samples of four sera which previously agglutinated the strain were still available and were retested. Now they also produced no agglutination. Since that time some 50 additional sera have been tested, but no further cases of non-specific agglutination have occurred. The suspensions, however, are still agglutinable to full titre when tested against immune rabbit serum.

Discussion

The agglutination of one strain of *L. icterohaemorrhagiae* by a number of sera which were negative with other strains, and the abrupt cessation of the phenomenon, seem to point to some temporary instability of this strain. It is of course well known that the agglutinability of strains varies greatly, and this strain was chosen because it agglutinated well. The medium used for culturing leptospira contains rabbit serum, and it sometimes happens that the serum of certain rabbits appears to retard rather than enhance the growth. Also, some apparently satisfactory cultures fail to agglutinate with specific antiserum. It might be argued, therefore, that some abnormality of the medium had produced unduly sensitive suspensions, whereas later subcultures in normal medium had reverted to their usual stability.

On the other hand there is the undoubted fact that the serum from only a proportion of cases of infective hepatitis gave positive results with these suspensions, and this seems to suggest that the sera possessed some unusual constituent which reacted with an abnormally unstable suspension.

Summary and Conclusions

More than 70 cases of jaundice occurring during the autumn of 1942 have been investigated. Of these, the sera of 34 agglutinated the strain of *L. icterohaemorrhagiae* (Jackson) that had been in use for eight years as a diagnostic antigen.

These "positive" sera failed to produce adhesion with the same strain, failed to agglutinate other strains of *L. icterohaemorrhagiae*, and failed to protect guinea-pigs against infection with a virulent culture of leptospira.

No leptospira were seen in the deposits of the centrifuged urine of these cases. Scarification of the deposits and inoculation of blood into guinea-pigs failed to produce infection.

Differential blood counts done on these patients were either normal or showed a relative mononuclear increase instead of the polymorphonuclear leucocytosis characteristic of Weil's disease.

The non-specific agglutinations are different from the false positives we have previously described. In our opinion they are due to an acquired abnormal susceptibility of the strain used as the antigen.

This instability was lost on further subculture, and the strain has apparently reverted to normal.

There must have been some additional factor present in the serum, because the sera of only a proportion of cases of jaundice produced this agglutination. Such an occurrence makes it necessary to employ cultures of more than one strain for diagnostic purposes.

We feel that this is an additional argument in favour of the view we have previously expressed that "until some method of standardizing cultures of leptospira is employed, the serological diagnosis of Weil's disease should be undertaken only at laboratories where the idiosyncrasies of the antigens are well known."

We wish to express our thanks to Col. W. H. O'Riordan, M.C., O.C. Cambridge Hospital, Aldershot, and to Lieut.-Col. N. T. Whitehead, M.C., R.A.M.C., assistant director of pathology, South-Eastern Command, for placing every facility at our disposal during this investigation.

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SYMPTOMATOLOGY OF MALARIA

BY

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Since April, 1942, I have been medical officer to a unit heavily exposed to malaria. During the hot months we had many cases of acute febrile malaria, 80% of which were malignant tertian infections. Hyperpyrexial, cerebral, and bilious forms were encountered, and one quickly grew accustomed to the vagaries and complications of malaria in its acute forms, and later to the so-called chronic malaria with its enlarged spleen, anaemia, and general ill-health.

With the onset of the cold weather fresh cases rapidly diminished, although I was faced with a large number of patients with relatively trivial complaints whom I at first treated on conservative orthodox lines according to their symptoms, but with no success. Headaches and pains in the back were evidently not English aches and pains. Dismissing the possibility of malingering by reason of my personal knowledge of the patients, I remembered that the largest pathological factor in this part of India was malaria, and, having access to a microscope, I began a general investigation of all cases reporting sick.

I hope, by recording the following cases, to show that malaria is something more than an acute febrile disease, and that it can produce such varied symptoms as pains in the back, rheumatic pains about joints, pains in the testicles, urticaria, multiple conjunctival ecchymosis, cardiac irregularity, recurrent diarrhoea, and obstinate eczematoid conditions without fever. I cannot say dogmatically that these symptoms and malaria are direct cause and effect, but I suggest that there is weighty evidence in favour of this, having regard to the positive blood examinations and the results of treatment.

Case Records

Case 1.—Complained of severe pain in the back, worse at rest than when walking about; no history of malaria; treated for several days as lumbago with liniment and mist. sod. sal. without improvement. A thick blood film showed B.T. rings and trophozoites; the spleen was not palpable though the splenic area was dull to percussion. A standard course was given and all symptoms disappeared on the third day of treatment.

Case 2.—He had severe pain over second costal cartilage on left side. This appeared swollen and was tender on pressure. There was also clinical evidence of anaemia and general ill-health. A thick blood film revealed M.T. rings; the spleen was not palpable. After a course of standard treatment all symptoms disappeared.

Case 3.—This patient had severe pain in left side of chest over fifth, sixth, and seventh ribs, worse on breathing. There was no fever and no physical sign in the chest. The tip of the spleen was palpable, and a thick film revealed M.T. rings and crescents. All symptoms subsided after a standard course.

Case 4.—Complained of recurrent swellings of the face; there was no history of any previous allergic phenomena. A blood slide revealed B.T. rings and trophozoites. After a standard course no further swellings occurred. A previous similar case had been seen in a patient with recurrent benign tertian malaria. This man had urticarial swellings of face and over both tibiae and above the ankle-joint. A third case showing B.T. rings has also been seen.

Case 5.—He developed a patch of dry scaly eczema with occasional formation of vesicles and pustules just above the left knee; other less-marked but recurring areas of dry scaling with erythema were apparent on the flexor aspects of the arms. Exposure to sun aggravated the condition. The spleen was not palpable, but thick