Summary and Conclusions

The sprue syndrome has been modified by war conditions in India, bringing into prominence certain aetiological and clinical features. Such aetiological points are: (*a*) There is a marked seasonal incidence reaching its peak in the month of June. (*b*) The condition is prevalent in Assam, North Burma, Bengal, Bihar, and less so in Bombay Presidency. Whether military or geographical factors have predominated in this incidence cannot be stated. (*c*) There is a surprising lack of positive relationship with dysentery regarding the monthly incidence and the incidence of dysentery previous to sprue, which is not greater than in normals, but one still retains the impression that in individual cases dysentery may unmask the latent sprue syndrome. (*d*) Suppressed or latent malaria exacerbates sprue. In such instances eradication of malarial infection rapidly improves the sprue syndrome. (*e*) A fair or a dark complexion bears no relation to the incidence of sprue, but fair men form a majority of severe cases. (*f*) Acute sprue has developed on a well-balanced diet under jungle warfare conditions. Palatability of diet is as urgent a physiological need as calories.

The clinical picture of acute sprue has been contrasted with that of the classical disease, not often seen in this series. The syndrome following dysentery and subacute hepatic necrosis is described, and emphasis laid on the borderline cases with glossitis or steatorrhoea dissociated.

The complete pictures of vitamin-deficiency syndromes have not been met with. Signs of A-deficiency were equivocal. Nicotinic acid deficiency has been more frequent than riboflavin deficiency. No evidence was found of deficiency of vitamins B_1, C, D, and K.

Faecal Fats.—The methods of collecting stools at present standard are inadequate. Three-day collections on known fat diet, with quantitative measure of stool fat per day, are essential for accuracy. The degree of steatorrhoea has little prognostic value.

Blood changes have rarely been severe. With the haemoglobin less than 12 g. %, hyperchromic anaemia was more frequent.

Prognosis as to life is good, but as to function it is poor. There is reason to believe that a large percentage will progress into the classical form unless liver therapy is continued.

From the above description it is clear that in sprue the whole alimentary tract from lips to anus is affected—the accent of the process falling on different regions at different times. We are entirely ignorant of the nature of this process, though we know it to be modified by liver, nicotinic acid, and riboflavin. Nor are we well informed as to the nature of the dysfunctions in digestion and absorption in this condition.

The frequency of remission and relapse and the dissociation of signs and symptoms make assessment of diet or drug therapy very difficult. Many more controlled observations are needed, and until these are forthcoming theorizing on sprue is like trying to do a jigsaw puzzle without most of the pieces.

Our thanks are due to the Director of Medical Services, India, for permission to publish this paper.

REFERENCES

Black, D. A. K., and Fourman, P. (1945). *Indian med. Gaz.* (in press).
Fairley, N. H. (1930). *Trans. roy. Soc. trop. Med. Hyg.*, **24**, 131.
—— (1936). Ibid., **30**, 15.
Manson-Bahr, Sir Philip (1943). *The Dysenteric Disorders*, London.
Napier, L. E. (1943). *The Principles and Practice of Tropical Medicine*, Calcutta.

The University Extension and Tutorial Classes Council, in co-operation with the Provisional National Council for Mental Health, is prepared to hold this year, provided sufficient applications are received, a course on educationally subnormal children and mental defectives. It is hoped that the course can take place, as in recent years, at the London School of Hygiene and Tropical Medicine, Keppel Street, Bloomsbury, and the date fixed is March 25 to April 5. Students will be required to arrange their own residence. The course is intended for medical practitioners, more especially those who are engaged as school medical officers and as certifying officers to local authorities under the Mental Deficiency Acts. Registration fee 10s. 6d., fee for course £5 15s. 6d. Intending candidates should apply at the earliest possible date, but in any case by Feb. 28. The registration fee must be paid at the time of application and the fee for the course before March 16. If applicants withdraw before this date the fee of £5 15s. 6d. will be returned or carried forward to another course as preferred. Should the course have to be cancelled all fees will be returned. Cheques should be made payable to the Provisional National Council for Mental Health, and crossed Barclays Bank Ltd. All communications with reference to the course should be addressed to: Miss Evelyn Fox, C.B.E., c/o University Extension Department, University of London, 39, Queen Anne Street, London, W.1.

OUTBREAK OF WEIL'S DISEASE IN THE BRITISH ARMY IN ITALY

PART I: CLINICAL STUDY

BY

JAMES H. HUTCHISON, O.B.E., M.D., M.R.C.P., F.R.F.P.S.
Lieut.-Col., R.A.M.C.; Officer Commanding Medical Division

J. S. PIPPARD, M.B., M.R.C.P.
Capt., R.A.M.C.; Graded Physician

AND

M. H. GLEESON-WHITE, M.B., B.S.
Major, R.A.M.C.; Pathologist

(From a Military Hospital, C.M.F.)

PART II: POST-MORTEM AND HISTOLOGICAL FINDINGS

BY

H. L. SHEEHAN, M.D., D.Sc., M.R.C.P.
Colonel, R.A.M.C.

(Abridged)

PART I
CLINICAL STUDY

Weil's disease was first proved to be caused by the *Leptospira icterohaemorrhagiae* by Inado, Ido, and others, in Japan, in November, 1914. Cases were described among British troops fighting in the rat-infested trenches of the Western Front (Dawson and Hume, 1916; Stokes, Ryle, and Tytler, 1917). Between the wars the disease was shown to be prevalent in certain parts of Great Britain among fish-workers (Davidson and Smith, 1939), sewer-workers, and others. About 25% of rats appear to be infected with the leptospira even in areas where the disease rarely appears (Hurst, 1941). During the recent war the disease has not been common among British troops, presumably because static trench warfare has not been a feature. An outbreak in the British Army in Normandy has been recorded by Bulmer (1945).

The outbreak described in this paper occurred in Italy among soldiers who had all been bathing in the River Arno and its tributaries, and in bomb craters, which were just behind our forward positions, during August and September, 1944. The majority of the cases (17 undoubted cases and 2 probables) were dealt with by this military hospital.

Clinical Picture

All the 17 undoubted cases ran a similar course. Onset was sudden, with general weakness, shivering and high fever, nausea, and sometimes vomiting. Severe headache was common at onset, although in some cases delayed for 24 to 36 hours. General muscular aching and stiffness commonly developed with progressive severity over the course of the next few days, sometimes rendering the patient incapable of unaided movement, and in a few cases requiring morphine for relief. This severe pain decreased when jaundice developed. Neck stiffness was complained of in 3 cases.

Intense conjunctival suffusion with a typical varicosity of the arterioles was constant and early in appearing, and tended to persist until the patient began to improve. Icterus developed between the 3rd and 8th days of the illness, in all but one mild case rapidly became very deep, and in every case had a remarkable orange-yellow tint, this colour presumably being due to jaundice in a skin flushed by general arteriolar dilatation. The icterus persisted for weeks, and assumed a more greenish colour as conjunctival and skin suffusion disappeared. Profound anorexia and distressing vomiting characterized the early icteric phase. Tachycardia was marked.

Haemorrhages were seen in every case in this series, varying in degree and situation. Haemorrhagic herpes occurred in 9 cases; petechiae and ecchymoses of skin and mucous membrane were invariably found; subconjunctival haemorrhages and epistaxes were common, and small pre-retinal haemorrhages were observed in 3 cases. Visceral bleeding—in one case frank haematuria—was common, and its severity was a factor in causing death in 5 fatal cases.

All the cases began with high fever (103–105° F.), which settled by rapid lysis as a rule. The duration of the fever, which was unrelated to the severity of the illness, was 5 to 12 days, save in one case in which it persisted for 26 days.

A striking feature of the illness, common to all cases and appearing at about the onset of the icteric phase, was some degree of oliguria; in 3 of the fatal cases and in 2 others this became anuria for a variable period. The urine contained a large quantity of albumin; granular casts and red blood cells were common microscopical findings. Specific gravity tended to remain constant at about 1010, and the amount of bilirubin was less than would have been expected from the severity of the jaundice. During this ictero-oliguric phase extreme prostration, mental torpor, and quiet delirium were the rule. During this phase also the blood urea figures were raised considerably (save in the one mild case). Death occurred in 5 cases between the 7th and 14th days of illness—in four from uraemia and in one from uraemia and massive pulmonary haemorrhage.

The spleen was palpable in 1 case and doubtfully so in 2 others. Hepatomegaly was inconstant and never great. Polymorphonuclear leucocytosis occurred in all save the one mild case during the acute stage of the disease.

Treatment

Specific therapy employed was penicillin in 6 and antileptospiral serum in 3 cases. When the first cases were diagnosed the only information available was that *L. icterohaemorrhagiae* was insensitive to penicillin *in vitro* (Abraham *et al.*, 1941). It was decided, however, to use penicillin in "orthodox" dosage and await results. The dosage in the 6 cases was 15,000 units three-hourly by the intramuscular route to a total of 600–660 thousand units. Unavoidably penicillin could not be started in the pre-icteric stage, but between the 6th and 10th days of illness. One patient treated on the 7th day died after 210,000 units. Five cases recovered after illnesses of great severity, not differing from those which did not receive specific treatment. The absence of any obvious benefit on the fever, toxaemia, icterus, pulse rate, or urinary output discouraged us from using heavier doses of a drug then scarce. Antileptospiral serum, also scarce, was used in 2 cases in doses of 60 c.cm. intravenously on the 7th and 8th and the 6th and 7th days of illness respectively, with 1 death; and in the third case, also fatal, 60 c.cm. was given only on the 7th day of illness. The serum had no obvious beneficial effect. In 8 cases (2 fatal) no specific therapy was used.

General measures were directed towards combating liver and renal failure. Fluids with added glucose were pushed by mouth, heavy doses of alkali given orally, and intravenous drip infusions of 3.3% glucose in 0.3% saline used as a routine. The impression was formed that unless oliguria can be rapidly abolished a fatal outcome is certain in this disease.

Laboratory Findings

[Here the authors acknowledged the help of three laboratories—No. 1 Central Pathological Laboratory, the Emergency Vaccine Laboratory U.K., and the laboratory of the British Traumatic Shock Research Team.]

Guinea-pigs were inoculated intraperitoneally with 5 c.cm. of blood taken from 15 of the cases on the 3rd to 11th days of illness, and with 10 c.cm. of urine (alkalinized) from the other 2 cases on the 13th and 16th days respectively. Eleven of the guinea-pigs remained well; the other 6 became ill, and of these 5 died, and at necropsy showed to a varying degree jaundice, haemorrhages into the abdominal viscera and retroperitoneal tissues, and the characteristic "butterfly" haemorrhages in the lungs. Leptospira were grown from the kidneys of 3 of them. From 13 of the 17 cases in this series serum was examined for leptospiral agglutinins, some being tested against local "Cartwright" strains, some against stock "Winjberg" strains, and some against both. No serious antigenic difference between the strains was demonstrated. All the sera gave a "positive" result at a conservative diagnostic level of titres of 1/300.

Total leucocyte and differential counts were carried out on all 17 patients between the 4th and 8th days of disease. A leucocytosis ranging from 11,000 to 34,000 per c.mm. was found in 10 cases; 5 in which the counts were below 10,000 reached levels of 13,000–20,000 by the 9th to the 15th day. In 12 of the 17 cases a blood urea estimation was carried out between the 5th and 15th days, and in 8 the figures obtained ranged from 150 to 288 mg. per 100 c.cm. There was evidence of some degree of nitrogen retention in all cases. The value of guinea-pig inoculation and the estimation of leptospiral agglutinins, total and differential leucocyte counts, and blood urea in the diagnosis of Weil's disease is amply supported.

Convalescence

Convalescence was slow in each of the 12 patients who recovered, and they were not considered fit for discharge to a convalescent depot until 17 to 20 weeks from the onset of their illness. During the convalescent period a series of investigations were made in an attempt to judge progress and to determine whether or not there was any permanent hepatic or renal damage.

With the exception of the one comparatively mild case, all showed a degree of anaemia. During the 4th week haemoglobins ranged from 70 to 80% (Haldane), with total red cell counts of between 3.5 and 4.5 millions per c.mm. This anaemia responded very slowly to iron therapy. The polymorphonuclear leucocytosis of the acute stage of infection disappeared during the 3rd and 4th weeks, and a total count below 10,000 per c.mm. with a relative lymphocytosis was common to all cases during the convalescent period. Sedimentation rates of between 20 and 40 mm. in 1 hour (corrected Wintrobe) were observed in all cases up to the 8th week, and figures of under 10 mm. were not encountered until the 10th week, thus confirming the slowness of convalescence.

Urea concentration tests were carried out between the 8th and 11th weeks of disease. In all but 3 cases a normal concentrating power was observed, and in these 3, on repeating the test later, the concentrating power was found to be satisfactory. Thus there was no evidence of gross renal damage as judged by the only renal function test readily available in the field. Hippuric acid liver function tests were carried out between the 8th and 15th weeks, and all but one case (and that case also on a later repetition of the test) gave results within the normal range. This again was the only suitable test available under field conditions, and showed no evidence of serious impairment of liver function.

Discussion

The 17 cases were all examples of the haemorrhagic form of the disease, and all but one were severe. Few diseases simulate the clinical picture outlined.

[Here the authors described other cases admitted to the wards in which the possibility of Weil's disease had to be seriously considered.]

During the period when the Weil's cases were in the wards over 1,800 cases of infective hepatitis were seen; but in only a very small minority, with fever, muscle-aching, conjunctival suffusion, and occasional neck rigidity, was Weil's disease really simulated, and it was felt that the possibility of confusion between Weil's disease and infective hepatitis is remote.

It is probable, however, that even severe cases of Weil's disease may occasionally run an atypical course. Such a case was one of two "probables" in this outbreak, in which the diagnosis was thought to be enteric fever with jaundice until, after the patient's recovery, the leptospiral agglutination results became available and the patient's serum taken on the 13th and 23rd days of illness showed a rising titre from *nil* to 1/1000 respectively. Such a case illustrates the difficulties which may confront the clinician in a country where Weil's disease, enteric fever with jaundice, malaria with jaundice, infective hepatitis (and even amoebic hepatitis combined therewith) may all occur at the same time.

The occurrence of non-icteric cases of Weil's disease has been recognized in previous outbreaks (Davidson and Smith, 1939); attention was called by Bulmer (1945) to the existence of such undiagnosed cases in the Normandy outbreak. The recognition of non-icteric cases depends on two factors: the suspicion that cases of P.U.O. may be instances of this disease, and the conversion of that suspicion into a certainty by serum agglutination reactions. The second "probable" case in this series, the diagnosis of which was not made until long after the patient's return to duty, was suspected because of the excessive severity of muscle-aching, a seven-day fever with one spot of herpes

which became ecchymotic, the arteriolar type of conjunctival suffusion which was seen in all the undoubted cases of Weil's disease, and the finding of bilirubinuria on one occasion on the eighth day of illness. Serum taken from this case on the ninth day of illness agglutinated *L. icterohaemorrhagiae* to a titre of 1/3000. Undoubtedly some of the milder P.U.O.s seen were also cases of Weil's disease. Clinical features which should arouse suspicion that a P.U.O. may be due to Weil's disease are: severe muscle pains, leucocytosis, arteriolar suffusion of conjunctivae, neck rigidity, and an after-rise of fever; evidence of renal damage is not to be expected in such mild leptospiral infections.

We are in complete agreement with the view of Bulmer (1945) that further trials of penicillin, used early and in heavy dosage, are indicated in this disease. Information has become available that some strains at least of *L. icterohaemorrhagiae* (Cartwright and Brown included: Alston, 1945) are sensitive to penicillin *in vitro* (Alston and Broom, 1944), and the same workers have demonstrated that penicillin may have a curative action on leptospiral infections in guinea-pigs.

[The authors in an epidemiological note then gave a description of the circumstances leading up to this outbreak of Weil's disease. The weather was hot and the troops in the neighbourhood of the Arno, which was at its lowest, with large stagnant pools along the partially dried-up bed, took every opportunity to bathe. The water-side rat population, swelled by an influx from the devastated built-up areas in the vicinity, were in great evidence, and thus large numbers of soldiers were constantly in contact with water freshly contaminated with rat urine, and, given a sufficiently high leptospiral carrier rate in the rats, conditions were favourable for an outbreak of Weil's disease.]

As soon as the first cases were diagnosed an embargo was placed on all unauthorized washing, bathing, and vehicle-washing sites, and these measures, assisted by a drop in temperature, brought the epidemic to an end. As to the leptospiral carrier rate of the rats in the area, at least two out of ten rats caught were found to be harbouring leptospira in their urinary tract. No cases were reported among civilians, although the Italian medical authorities stated that Weil's disease not infrequently occurred in persons bathing in the Arno and Tiber. A surprising feature was the apparent immunity of the Indian troops in the area, although, if anything, they washed and bathed with total immersion more often than the British troops. This recalls their striking resistance to diphtheria, and is another example of an apparent racial immunity to a particular disease.

PART II

POST-MORTEM AND HISTOLOGICAL FINDINGS

This report is based on the necropsy and histological findings in 6 cases* from the epidemic. Ashe, Pratt-Thomas, and Kumpe (1941) discussed the pathology in a review of the literature on Weil's disease. Some of the lesions they describe appear to be terminal or autolytic; others are in agreement with the present findings.

Every case had deep icterus of the skin and other tissues usually affected in jaundice. The haemorrhages were petechial. The liver was of normal size or slightly enlarged, and, apart from jaundice, showed no abnormality to the naked eye. Microscopically there was never any trace of recent or healing necrosis nor of degeneration of liver cells. The chief matters of interest were progressive changes in pigment deposition and in the appearance of nuclei.

Two patients dying at 6 and 9 days had apparently normal livers. Two dying at 10 days had occasional small round masses of bile pigment in the bile canaliculi of the centrolobular part of the liver columns and a moderate amount of granular pigment in this area. The liver cells had a moderate number of double and of very large nuclei and rather numerous mitoses. Two patients dying at 13 and 15 days had much bile pigment centrolobularly and numerous double and very large nuclei, but only scanty mitoses.

The kidneys were somewhat enlarged; cortex rather broad and moderately bile-stained; medulla pale. Microscopically the glomeruli showed no abnormalities.

The first convoluted tubules had finely granular cytoplasm, tending in later cases to be bile-stained and rather foamy. The second convoluted tubules always contained many casts. The collecting tubules were also obstructed by casts in every case, particularly marked in the papillary portion of the medulla. The epithelium of these tubules showed considerable alterations. In a patient who died at 6 days it was very swollen, with many pyknotic nuclei; in one at 9 days the swelling was much less, and the number of nuclei considerably increased in the areas of proliferation; in one at 15 days the cytoplasm was still unduly dense and occasional pyknotic nuclei were still present. The intermediate zone always showed a considerable number of monocytes distributed diffusely, but with some foci of increased density. At 6 days these cells were nearly all of large mononuclear and plasma cell type, mainly collected in very thin-walled vessels; in later cases the larger cells in the vessels became less numerous, but there was an accumulation of smaller monocytes in the interstitial tissues of the zone.

In 4 cases there was a gross haemorrhagic bronchopneumonia; in 2 a gross haemorrhagic oedema of the submucosa of one or two loops of small intestine, and an acute ulcerative colitis in a third. In 2 cases the skeletal muscles and myocardium were deep purple in colour but showed no microscopical abnormality. Abnormalities in other organs were slight or not relevant.

* Part I mentions only 5 deaths. Presumably the sixth was one of a different series.

Discussion

The entire absence of necrosis in the liver is of interest. It appears that for about the first 9 days of the disease there is some functional interference with the secretion of bile; after this the liver cells take up their function again, but the bile canaliculi in the liver columns are not able to drain the centrolobular cells adequately, and bile thrombi are built up there. The prominent lesions in the kidneys are the cast obstruction and epithelial damage to the collecting tubules and also in the second convoluted tubules, and the monocytic infiltration of the intermediate zone.

Some light is thrown on the functional significance of these renal changes by the histological lesions found in severe haemolytic reactions following transfusion.

[Here the author described the renal changes in three patients who became jaundiced after transfusion and died of uraemia. The histological appearances of the kidneys were indistinguishable from those in one of the cases of Weil's disease which had ended fatally in 6 days.]

This similarity between the appearances of the kidney in Weil's disease and in haemolytic transfusion reactions raises three possibilities for consideration: (*a*) that the casts have the same haemolytic origin in both cases; (*b*) that in both cases the oliguria and uraemia are due to a combination of cast obstruction and of epithelial damage to the collecting tubules; and (*c*) that the monocytic infiltration of small vessels and capillaries in the intermediate zone in both cases is related to drainage from interstitial tissue around the damaged medullary tubules.

Summary

Part I.—An outbreak of Weil's disease in Italy during Aug. and Sept., 1944, is described, and the clinical and pathological findings in 17 proved cases recorded and commented upon. Treatment is discussed with special reference to penicillin, which was used, without benefit, in 6 cases; a trial with larger dosage is urged. Difficulties in differential diagnosis are discussed. Laboratory investigations during convalescence are summarized and the circumstances in which the outbreak occurred are reviewed.

Part II.—Post-mortem and histological findings in 6 fatal cases are described, and emphasis is laid on renal changes—with their resemblance to those seen in fatal haemolytic transfusion reactions—and the absence of histological evidence of gross hepatic damage.

Thanks are due to Col. G. G. Drummond, R.A.M.C., for permission to publish these cases; to Brig. E. R. Boland, O.B.E., R.A.M.C., for his interest and encouragement; to Major A. Jordan and Capt. C. Giles, R.A.M.C., of No. 1 Central Pathological Laboratory, C.M.F.; to the British Traumatic Shock Research Team; to Major Buckland, of the Emergency Vaccine Laboratory, U.K.; to Capt. R. W. P. Johnson, R.A.M.C., and Capt. B. S. Tulloch, R.A.M.C., for tissues; to the medical specialists of forward units for their clinical notes; to Miss E. B. Melrose and Miss S. Walsh, S/Q.A.I.M.N.S./R., for their skilful nursing of the cases; and to Sgt. L. Beaney, R.A.M.C., for his technical assistance.

BIBLIOGRAPHY

Abraham, E. P., *et al.* (1941). *Lancet*, **2**, 177.
Alston, J. (1945). Personal communication.
—— and Broom, J. C. (1944). *British Medical Journal*, **2**, 718.
Ashe, W. F., Pratt-Thomas, H. R., and Kumpe, C. W. (1941). *Medicine*, **20**, 145.
Bulmer, E. (1945). *British Medical Journal*, **1**, 113.
Davidson, L. S. P., and Smith, J. (1939). Ibid., **2**, 753.
Dawson, Sir B., and Hume, W. E. (1916). *Quart. J. Med.*, **10**, 90.
Hurst, Sir A. (1941). *Medical Diseases of War*, 2nd ed., p. 239, London.
Stokes, A., Ryle, J. A., and Tytler, W. H. (1917). *Lancet*, **1**, 142.