setback in specific treatment. Sanatoria had expanded in number and developed in scope, both for pulmonary and for non-pulmonary cases. In Britain the National Tuberculosis Scheme, inaugurated in 1912, had proved its worth. Artificial pneumothorax and other forms of collapse therapy had come into their own, particularly from 1920 onwards, when radiographic control became reasonably practicable. Much greater emphasis was being laid upon preventing the disease by reduction of contagion and by insistence on contact examinations. The understanding of the immunology and epidemiology of tuberculous infection had been advanced by the work of Ghon, Opie, Cummins, and many others.

[*Part II, with a full list of references, will appear in our next issue.*]

WEIL'S DISEASE: A RARE CONDITION?

BY

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An attempt is here made to establish a number of conclusions relating to this disease, which is still generally regarded as of academic interest only. In the first place, we are convinced that the infection is not by any means a rare one, nor is it likely to be encountered only by those whose work brings them into contact with certain industrial groups, such as sewer workers and miners. Secondly, we believe that it is not unreasonable to expect a diagnosis to be made within the first few days of the illness upon clinical methods alone, and that the only requirements are a familiarity with the characteristic picture as seen at this stage of the disease and a knowledge of a number of special points to be looked for and of simple laboratory investigations which must be carried out. Thirdly, as a result of our early recognition of suspected cases we have had the opportunity of watching the effect of specific treatment given at this stage of the infection, and our observations have left a feeling of confidence that this is of real value and may even be life-saving. Finally, as a result of considerable familiarity with the condition, a number of observations have been made which we believe have not been recorded before. We feel that a note on these may be of value.

Frequency of the Disease

In July, 1936, when Weil's disease was to us nothing more than an almost forgotten name, a case came under our care which proved to be a very typical example of this illness. A year later a second case was recognized, and by June, 1938, we had dealt with four such cases. These four cases were of particular local interest, for it appeared that in each case infection had been the result of bathing or working in the same stream (Robertson, 1938). During the next seven years a further 30 cases have been seen—that is to say, we have been encountering the condition four or five times every year.

So far as we have been able to ascertain, the total number of cases recognized during this time in the area in which our work is carried out has certainly not exceeded 40. These rather remarkable figures can surely indicate only two things: the relative frequency of the infection, and the ease with which it has been able to evade recognition.

Recognition

Excellent accounts of the clinical picture are available in textbooks and have been elaborated by numerous workers elsewhere, so that only a brief reference to this is needed here. The infecting organism, *Leptospira icterohaemorrhagiae,* is carried by the rat, and it can be assumed that something like 40% of all rats are infected. The leptospira leaves its host by way of the animal's renal tract. Human infection occurs as the result of contact with water which has been contaminated by rats' urine. Only fresh water can become infective, as quite small amounts of salt render the organism inactive; while direct sunlight has a similar tendency. Stagnant water is more dangerous than that of a freely flowing stream. Under these conditions the leptospira can probably survive indefinitely. The incubation period appears to be about ten days.

No age is immune, and we have seen the disease at all ages from 5 to 78 years. Characteristically, the onset is abrupt and the victim has been in good health. The symptoms are high fever, often a rigor, severe headache, generalized pains, not infrequently gastro-intestinal symptoms, haemorrhages from some part of the body, and in about half the cases jaundice of varying degree after the fourth or fifth day. In some of the more severe and jaundiced cases serious renal impairment appears, with an increasing retention of nitrogen, sometimes terminating in anuria. It is in this group of cases that fatalities occur.

It must be emphasized that half the cases, whether treated early or not, show no jaundice at any stage of the illness, and among these the incidence of a lymphocytic leptomeningitis is very high. Probably all cases show a peculiar conjunctival suffusion at some time, though this may be transient and may be missed.

Of particular significance are the muscle pains. These are often intense and may persist for several days. The pains are in muscle and are not related to the joints. During this phase pressure over muscle, particularly in the limbs, is often intolerable, and this objective finding almost always persists for several days after the subjective symptoms have subsided.

The headache is severe and by its occipital predilection suggests meningeal involvement; this is often further emphasized by the presence of neck rigidity and a positive Kernig's sign. These findings usually make lumbar puncture inevitable; indeed, several of our cases reached us with the diagnosis of meningitis already made. The cerebrospinal fluid is frequently under pressure and is always water-clear. Pathological examination even in a case with very pronounced meningism may be quite normal when the routine tests are applied; but more often there is slight increase in protein, with a pleocytosis which may reach several hundred cells per cubic millimetre. The sodium chloride level is always normal. If the urea content of the fluid is investigated it is found invariably to be raised above the level which would be regarded as normal for the patient's age. In the laboratory which carries out most of our work the urea content is determined in all lymphocytic fluids which show a normal amount of chloride. This simple arrangement has been of great help in detecting a few early cases.

Haemorrhages are seen at some stage of the illness in most cases, and these may appear early. They may be from the nose, the gums, the gastro-intestinal tract, or into the skin and mucous membranes. When herpes labialis is present it is often haemorrhagic. In some cases a curious mottled appearance of the palate is seen; this was first pointed out to us by Dr. Evan Jones, and has been seen four times. It has not been possible by haematological investigation to determine the cause of this tendency to bleed. Bleeding times, clotting times, and platelet counts have always been normal; the prothrombin level has not been estimated in our cases.

The *urine* usually shows the presence of albumin, often cylindruria is observed, and not infrequently red cells are present, but a normal urine does not exclude the diagnosis. Often the *white cell* count is unaltered in the first few days. This statement is the reverse of what has usually been recorded, but time and again we have noted this normality. When jaundice has appeared the rule is a polynuclear leucocytosis, thus helping to differentiate leptospiral jaundice from that due to infective hepatitis. By far the most important single pathological investigation is undoubtedly the determination of the *blood urea* level. In all our cases this has been raised from the earliest stages, and the level to which this has reached has always provided a useful indication of the severity of the infection.

It should be possible to detect the infecting organism in the blood stream during the first five or six days of the illness, either by direct examination of blood smears with dark-ground illumination methods, or by animal inoculation of the infected blood. We have been successful only once in this, and then by the latter method. It is our view that these diagnostic methods are unnecessary.

Finally, when suspicion has been aroused, a most careful inquiry into the patient's work, home surroundings, and habits with regard to bathing, etc., in fresh water must be made. In nearly all our cases there has been some quite obvious source of possible infection; and in those suspicious cases where no such possibility has been obvious we have almost always failed to prove the diagnosis. We regard this part of the investigation of cases as of the utmost importance.

It is well known that during the septicaemic stage of the illness—that is to say, during the first five or six days—antibodies upon which the diagnostic agglutination reaction depends have not developed in sufficient amount to give a positive finding even at the lowest dilutions. It is therefore useless to expect such a finding until after this stage is over.

At this point I would like to record our deep appreciation of the help we have received from Dr. J. C. Broom and his colleagues of the Wellcome Research Institution, who have carried out all our serum testing for us.

At the appropriate time blood has been sent to Dr. Broom for agglutination testing. Where possible, samples have been forwarded at intervals. This has been done for two reasons. In the first place, a rising titre at which agglutination can be demonstrated is clearly of more diagnostic value than any single test, and, in the second place, we have observed that in the more severe cases the first positive finding has not appeared at the usual time—that is to say, the fifth or sixth day—but has been delayed for several days. In one fatal case the test was negative on the 9th day but positive 1 : 100 on the 11th, death ensuing on the following day. In another fatal case the test was negative on the day of admission to hospital—the 7th day of illness—positive 1 : 30 on the 8th day, 1 : 100 on the 9th, and 1 : 300 on the 10th, the day of death. In yet another case seen recently the patient's serum showed a mere trace on the 8th day but was positive 1 : 300 three days later, when heart blood was taken as the patient was actually breathing his last.

We have been quite unsuccessful when attempting to demonstrate the leptospira in patients' urine. It should be possible to do this for varying lengths of time after the first week; but the urine must be freshly passed and neutral in reaction.

Personal Diagnostic Experience

With growing familiarity with the disease an increasing number of cases are diagnosed early. About 70% of our cases were suspected within forty-eight hours of being seen. Some of these cannot qualify as early cases as they did not reach us until late in the illness. Nearly 50% of our cases have been diagnosed within the first four days of the illness and specific treatment started. We believe that this facility in diagnosis is rapidly achieved after quite brief contact with the condition: succeeding house-physicians very rarely failed to detect suspicious cases, and after leaving our district they continued to make the diagnosis with accuracy in other places.

Dr. Broom, in a personal communication, mentions that he has on a number of occasions noticed that positive sera have been received in his laboratories from districts where previously the infection had not been noted, only to find that these sera have been sent to him by doctors who had worked as colleagues with us in this district.

Treatment

Writer after writer has lamented that specific treatment in the early stage of the illness is almost impossible because of diagnostic difficulties. Hutchison, Pippard, Gleeson-White, and Sheehan (1946), record the treatment with penicillin of 6 out of 17 cases appearing in British soldiers in Italy. They state that "unavoidably penicillin could not be started in the pre-icteric stage, but between the 6th and 10th days of the illness." In 1934 Davidson *et al.* wrote: "Hence it appears to us that the clinical diagnosis in the early stage, before jaundice occurs, presents almost insuperable difficulties. Accordingly the full benefit of serum treatment is unlikely to be realized."

Of our cases 12 have been given specific antileptospiral serum during the first four days of the illness, and one other received penicillin within the first two days. In this group there has been no mortality. This compares favourably with the remainder of our cases—about a score—none of which received treatment until after the fourth day, and among which there were six fatalities—a mortality of 30%.

The story of one very severe case seems to support our impression that serum given early can influence the infection.

In October, 1942, Mrs. F., aged 20, who had had an attack of abortus fever ten months previously, was admitted after three days' high fever. She was very ill, and our investigations seemed to support our suspicion that she was suffering from Weil's disease. Intensive intravenous serum treatment was started at once. She became jaundiced two days later, and finally anuric with a blood urea of 295 mg. per 100 ml. Certain special measures, which will be referred to later, were instituted in an attempt to re-establish renal function. These were successful. She had received 480 ml. of serum, all given intravenously. A week later there was an abrupt rise of temperature with clinical deterioration. The titre of her abortus reaction rose steeply, and it was thought that possibly her old infection had been reactivated. Consequently she was treated with intramuscular "soluseptasine." As this failed to produce the usual rapid reduction of the fever we were driven to the conclusion that her relapse represented the commonly seen secondary rise of Weil's disease. She was desensitized and further intravenous serum given—in all 280 ml. Her fever fell by crisis in twenty-four hours, and she gave no further anxiety.

Penicillin

Alston and Broom (1944) reported that nine strains of *L. icterohaemorrhagiae* and one of *L. canicola* were found to be sensitive to penicillin *in vitro*, and that penicillin exerted a protective action in guinea-pigs infected with leptospira provided treatment was started within twenty-four hours of infection.

Lloyd Hart (1944) reported the rapid disappearance of organisms from a patient's urine after the use of penicillin given late in the illness; and Baldry, in a personal communication, stated that a severe case was treated with penicillin rather late in the illness, apparently with immediate improvement, followed by deterioration when penicillin was withdrawn, and subsequent complete recovery consequent upon the re-establishment of penicillin treatment in larger doses. In the Italian cases already referred to the workers were not impressed by the effect of penicillin given in the icteric stage.

On July 24, 1945, a boy aged 8 years was sent into hospital as a suspected case of Weil's infection by Dr. Loveless, of Stockbridge. He had been ill for forty-eight hours. Our own examination and investigations proved the suspicion to be correct by the finding of a strongly positive agglutination reaction. Penicillin in 20,000-unit doses was given every three hours from July 24 to 28. The boy's temperature, which was 103° F. (39.4° C.) on admission, was normal within twenty-four hours. His blood urea, which had been 65 mg. per 100 ml. on admission, had fallen to 35 mg. by the 29th, and he was discharged from hospital in full health on Aug. 1. No observations of any importance were subsequently made.

Little can be judged from a single case, but it should be noted that the infection appeared to be a severe one, as judged both by the clinical condition and by the blood urea level of 65 mg. per 100 ml. within forty-eight hours of the onset. Furthermore, in spite of this, his fever lasted only three days, as compared with the usual five or six days, and he developed no icterus. One was certainly left with the impression that a severe case had made an unexpectedly rapid recovery. Penicillin was given to two other late cases, when icterus had been established for several days and nitrogen retention had become extreme, with no suggestion of benefit. In one other case, mentioned on page 812, penicillin was given on the sixth day after serum had failed to influence an unusually prolonged febrile stage. The temperature fell by crisis, but there was no clinical improvement, and the boy died the next day, non-icteric.

A farmer of 53, seen in October, 1946, had been treated with 50,000 units of peniciilin every four hours from the second day of an acute febrile illness. He became anuric on the seventh day and secreted no urine for 36 hours. Clinical jaundice was not present. When I saw him, on the ninth day, diuresis had set in and his temperature had subsided. A petechial rash, haemorrhagic herpes, and slight conjunctival icterus suggested that he was suffering from Weil's disease. His blood urea on that day was 250 mg. per 100 ml. and he had an icteric index of 11 units. His blood agglutinated leptospira up to a dilution of 1:1,000. There was no further rise in his icteric index, and he has made a good recovery.

The importance of this case appears to be the suggestion that the penicillin had protected his liver while failing to prevent

the renal complications. We have never seen blood urea figures approaching 250 mg. in any case which was not frankly jaundiced, except for the fatal case reported in this paper.

These observations, taken with the experimental evidence reported by Alston and Broom, strengthen our belief that, provided it can be used during the early septicaemic stage and that it is used freely, we have in penicillin a specific of probably greater usefulness than serum. It may well be that the best results will be obtained by a combination of both agents.

Other Points about Treatment

In addition to the questions relating to specific treatment, a number of observations have been possible with regard to the more general aspects of treatment. Immediately a diagnosis has been made—indeed, when it remains only a suspicion—the patient should be put on a low-protein diet. Fluids should be pressed and glucose used freely. The urine should be rendered alkaline by the use of potassium citrate, and a very careful intake and output record should be kept for each twelve hours. At the first sign of a falling output more drastic measures to overcome this should immediately be started. We have found valuable the free use of 50% glucose intravenously, and it is our habit to give 50 ml. every eight hours. We have not hesitated to employ continuous intravenous drip methods, using saline, glucose-saline, plain glucose, and sodium sulphate, great care being taken to maintain a proper salt balance in order to avoid pulmonary complications. This last is of particular importance, as the bad cases have frequently shown pulmonary congestion, and even consolidation, quite apart from intravenous therapy. We have used heat and even short-wave diathermy to the renal areas, and have brought heat to the kidneys from in front by means of hot colonic irrigation as suggested by Hamilton Fairley.

Finally, we have in three desperate cases attempted by the use of high spinal analgesia to re-establish renal function by invoking sympathetic release. In each of these three cases the anuric state gave place to secretion following the spinal analgesic. In one—Mrs. F., already referred to—this went on to full renal function and complete recovery; but in the other two, both of whom showed blood urea figures of over 500 mg. per 100 ml., in spite of restarting secretion recovery did not follow. One of these men excreted 30 oz. (0.85 l.) of urine on the day before death, and his blood urea had fallen.

The value of high spinal analgesia in certain cases of anuria was well shown in the case of a 5-year-old girl who had sustained an extensive third-degree burn of the thigh. Five days after her accident she was found to be completely anuric and her blood urea had reached 520 mg. per 100 ml. Three days later, after complete failure of all other methods of treatment, high spinal analgesia was induced, with subsequent re-establishment of renal function and ultimate total recovery. In using this drastic method of treatment anxiety is bound to be experienced, as these cases invariably have a very low systolic pressure. Figures as low as 70 mm. Hg systolic have been seen. We have used injections of ephedrine before and during the treatment. In future we propose to use this method earlier in the threatening cases rather than leave it as a last almost hopeless attempt to save life.

It seems clear that the anuric state seen in the more severe cases will have to be regarded as an example of what Maegraith and others (1945) have called the "renal anoxia syndrome"; the appearance, naked-eye and microscopical, of the kidneys in fatal cases being to all intents and purposes identical with that seen in conditions such as crush syndrome, blackwater fever, incompatible blood transfusion, and so-called traumatic uraemia.

The part, if any, played by spinal analgesia or splanchnic block in the therapy of this condition is not as yet clear, but it should be recalled that in discussing this syndrome following trauma Trueta suggests the possibility that vascular spasm is in part responsible. Our results with spinal analgesia would seem to support this suggestion.

Serum Diagnosis

The final diagnosis in our cases has always rested upon the demonstration of agglutinins, if possible in rising titre, in the patient's blood. It has been suggested from time to time that where specific serum has been given this may influence such investigations, possibly falsifying diagnosis. This possibility is freely admitted, though in 1934 Schüffner, speaking of individuals incorrectly treated with serum and later proved not to be suffering from leptospiral infection, stated that in these people the agglutination reaction remained negative.

Alston (1940) carried out an experiment with rabbits in an attempt to determine the fate of specific antileptospiral serum. In four animals used, a positive agglutination reaction was obtained immediately after a test dose of serum. The titre of this reaction subsequently fell rapidly, and at the end of 120 hours antibodies could no longer be detected. In an attempt to repeat this experiment in the human subject 100 ml. of antileptospiral serum was injected intravenously into a patient suffering from influenza. Blood was tested for the presence of agglutinins at intervals of five minutes, one hour, twelve hours, and twenty-four hours after the serum injection. Though they were present in considerable concentration at five minutes and one hour, there was a steep reduction at twelve hours, and at twenty-four hours they had almost disappeared from the blood. In our case a dose equivalent to about three times the dose used by Alston, and considerably in excess of the usual therapeutic dose, was given, while the fall in titre seems to have been even more rapid than in the animal experiment. If more than one test is carried out, and a rising titre is obtained, we feel that this possibly disturbing factor in diagnosis can be safely discounted.

It must be remembered that a previous infection may be responsible for a positive agglutination reaction. Our first two cases had positive agglutination three and four years respectively after their illness, though not in high dilution. In such a case a rising titre would be required to establish the diagnosis, though, so far as we know, no case of second attack has ever been recorded.

Schüffner's often-quoted dictum, that where there is no icterus there is no mortality in this illness, is almost invariably correct. Indeed, we can find no reference to any fatal non-icteric case from the British Isles. This makes the following story seem worthy of mention:

In November, 1944, a boy of 15 was admitted to hospital on the surgical side with a tentative diagnosis of acute appendicitis. He had then been ill for three days and his temperature was 103° F. (39.4° C.). His white cell count showed 4,700 leucocytes with a normal differential count. His temperature was maintained, and three days later we were asked to see him as he had developed a generalized rash, and the question of measles had been raised.

Upon examination he was clearly very ill. The rash was morbilliform and generalized, but the buccal mucosa showed no changes. Furthermore, he had had measles three years before. His white cell count had risen to 12,700, with 95% of polynuclears. His blood urea was 73 mg. per 100 ml., and the icteric index 4 units; the urine showed a cloud of albumin only.

This was now the sixth day of his illness and blood was sent to Dr. Broom for testing. This first sample gave a very weak positive reaction at 1:10. Serum treatment had been started at once, but the boy's condition had deteriorated by the next day and his blood urea had reached 146 mg. per 100 ml. His temperature showed no sign of falling. Penicillin was substituted for serum, and though his temperature became normal in about 12 hours he continued to go downhill, and died on the eighth day of illness.

Two subsequent agglutination tests were both positive at 1:10 and 1:30 respectively. At no time was any suggestion of jaundice noticed, and his icteric index remained within normal limits.

Dr. Broom, in a personal communication, says that he has sometimes seen guinea-pigs infected with leptospira die very quickly and without the development of either jaundice or haemorrhages, as if they had been overwhelmed by the toxaemia before there had been time to develop the usual signs. Such, we feel, must have been the experience of this boy. Unfortunately it was not possible to carry out a necropsy in his case.

Weil's disease is not included in the schedule of diseases which call for notification under the Industrial Diseases Act in England, but in cases where it is possible to establish that the victim contracted his infection while at work the employer's liability under the Workmen's Compensation Act is obvious. In one of our fatal cases, that of a farm labourer who had been employed in thatching ricks about the time when he probably became infected, the judge in the Winchester County Court supported the claims of the appellants, and the man's widow

was granted a considerable sum in compensation for the loss of her husband. In two subsequent fatal cases, and under almost identical circumstances, it appears that the insurance companies concerned do not propose to question their liability, though a careful scrutiny of the cases has been made from the diagnostic aspect. Thus the need for solid and unquestionable diagnosis in these cases becomes of more than purely medical and scientific interest.

Since the writing of this paper Williams has treated a severe case of Weil's disease in a man of 53, deeply jaundiced, oliguric, and with a blood urea of over 300 mg. per 100 ml., by methods devised to raise the blood pressure—intravenous plasma and injections of ephedrine, combined with high spinal analgesia. The result was dramatic. There was no further increase in blood urea, and within twelve hours a considerable diuresis had been established which went on to a veritable deluge, with rapidly falling blood urea and uninterrupted recovery. This case, as judged by all the standards which our experience in the past had led us to accept as of importance prognostically—age, depth of jaundice, degree of nitrogen retention, and absence of early specific treatment—caused us to predict a fatal outcome. This prognostication was triumphantly disproved by the course of the illness.

No case has come under our care since the publication of Zondek's (1946) stimulating paper on extrarenal azotaemia and extrarenal uraemia, so that we have had no opportunity of investigating his suggestions with regard to Weil's disease, though we have fully confirmed his findings in severe gastro-intestinal bleeding and relapsed pernicious anaemia, in which the normal relationship between the urea and chloride excretion has been grossly disturbed in the direction of relatively reduced chloride excretion. Nevertheless, we feel confident that his findings would almost certainly be available in these cases, as the urea content in the urine of oliguric patients has always been above 2%.

Our observations in this disease lead us to believe that the mechanism of cortical renal ischaemia, as described by Trueta and others (1946), is of great importance in the aetiology of the syndrome of water and nitrogen retention seen in the more severe cases of this infection, and the explanation of the apparent success of spinal analgesia in these cases becomes more easily understandable. This work appears to emphasize the need for earlier use of this method of treatment in oliguric cases.

I would like to record again my sense of indebtedness to Dr. J. C. Broom for all his help and encouragement in this work. Dr. Wrigley, Honorary Pathologist, Royal Hampshire County Hospital, has been responsible for all the other pathological work done in our cases, and my sincere thanks are due to him. I am most grateful to numerous house-physicians for their help, and to the local practitioners who have been responsible for referring cases to me.

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In pursuance of the statutory procedure under the Factories Act, 1937, the Minister of Labour and National Service proposes to make, under Section 65, regulations entitled the Dangerous Occurrence (Notification) Regulations, 1946. The Dangerous Occurrences (Notification) Order, 1935, which would be revoked, extended the provisions with regard to notice of accident to the same classes of occurrences as are specified in the Schedule to these Regulations. The Order was, however, limited to factories or workshops within the meaning of the Factory and Workshop Act, 1901, and places which, for the purpose of the provisions of that Act with respect to accidents, were a factory or workshop or were part of the factory or workshop. The proposed Regulations require notification of the same classes of occurrences happening in factories as defined in the Factories Act, 1937, or in premises or places, or in the carrying on of processes or operations or work, to which Part V of that Act (which relates to the notification and investigation of accidents and industrial diseases) is applied by Sections 103 to 108. Copies of the Regulations may be had from H.M. Stationery Office or through any bookseller, price 1d.

AN UNUSUAL CASE OF WEIL'S DISEASE

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Evidence is accumulating which indicates that Weil's disease is not rare in this country. Gardner and Wylie (1946) report that over the past six years they have examined 182 sera which gave positive serological evidence of Weil's disease, and also that in various laboratories throughout Great Britain and Northern Ireland 488 cases have been serologically diagnosed during this period. It is probable that many mild and anicteric cases have escaped diagnosis. The present case is being recorded in order to stress the need to consider Weil's disease in the differential diagnosis of any case of jaundice or nephritis, and to report the occurrence of the clinical syndrome of bilateral adrenal haemorrhages in Weil's disease.

Case History

The patient, a heavily built man aged 56, was a butcher living in a village twenty miles from Manchester. For some days before the onset of his illness he had felt unusually tired, but continued normally with his work. On Oct. 25, 1945, he had a severe frontal headache, and the next day, having developed a high fever, he sought medical advice. On Oct. 29, the fever having persisted, a course of sulphapyridine was started, a total of 16 g. being given in four-hourly doses. On this day he began to vomit frequently, and, in his own words, "it has been a case of drink and vomit since." The vomitus became greenish black with a foul smell, and was described by a visiting relative "as if his motions were coming up the wrong way." In view of the vomiting it is difficult to say how much of the sulphapyridine was retained. On Oct. 30 jaundice started, and the patient was troubled by a persistent hiccup. No urine had been passed since Oct. 28, apart from a few drops of blood-stained fluid, and he had been constipated throughout the illness except for a small dark stool on Oct. 30.

The patient was admitted to the Manchester Royal Infirmary on the evening of the 31st, and died twenty hours later. On admission he was mentally clear but extremely anxious; retching and hiccup were frequent, and he complained of an intense thirst. The temperature was 96° F. (35.6° C.), pulse 130, and respirations shallow at 30 to the minute. On examination the most striking feature was jaundice. There was severe circulatory collapse, the pulse was thready, the extremities were very cold, and the systolic blood pressure was only 80 mm. Sweating was profuse yet dehydration was severe. The tongue was dry but clean, and the conjunctivae were congested. The pupils were constricted, probably as a result of morphine given before the journey to hospital.

Examination of the abdomen revealed numerous small purple petechiae on both flanks. No marked distension or rigidity was observed, but there was great tenderness. The liver was not felt—in fact, it seemed as if the area of liver dullness was diminished. No significant physical signs were found in the chest or central nervous system. A provisional diagnosis of acute hepatic necrosis or hepato-renal syndrome was made. Soon after admission it was pointed out that, apart from the jaundice, the general picture suggested acute adrenal insufficiency as in the Waterhouse-Friederichsen syndrome. There was also the possibility that the sulphapyridine administered might be implicated to some degree. Intravenous glucose-saline was given; unfortunately cortin was not available. The white cells numbered 14,200 and the haemoglobin was 13.5 g.%. The next morning he passed half an ounce (14 ml.) of urine, but the state of circulatory collapse continued.

The possibility of leptospiral infection was meantime considered and blood was taken for serological and biochemical investigation. The patient now lapsed into a state of muttering delirium, the pulse weakened and became imperceptible, the temperature rose to 100° F. (37.8° C.), and he died twenty hours after admission.

Laboratory investigations on Nov. 1 showed: W.B.C., 10,600 per c.mm. (polymorphs 76.5%, lymphocytes 10%, monocytes 3.5%, eosinophils 0.5%, myelocytes 6%, metamyelocytes 3%, Türk cells 0.5%, plasma cells 1%, nucleated R.B.C. 5/100 W.B.C.). Haemoglobin, 12.1 g. %. Blood urea, 270 mg. per 100 ml. Whole blood chlorides, 316 mg. per 100 ml. (as NaCl). Serum colloidal gold reaction: 2332110000. Van den Bergh test: immediate direct reaction with maximum colour in two minutes (bilirubin 32 mg. per 100 ml.). Serum proteins: albumin, 3.2 g. %, globulin, 3 g. %. Urine: centrifuged deposit showed numerous red cells and pus