BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 22 1951

LEPTOSPIROSIS IN ENGLAND AND WALES*

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Human leptospirosis is not a disease which presents the dramatic situations demanding instant action provided by sweeping epidemics of, say, plague and cholera. On the contrary, it is an insidious infection which has crept into our midst and has established itself almost unnoticed. It is recognized as a hazard attached to certain occupations, such as coal-mining and work in sewers, but the affection claims a toll of victims from other sections of the population—and does so almost unperceived.

It is perhaps natural for us to think of leptospirosis mainly as a group of diseases affecting man and some of his domestic animals. In fact, however, leptospires are primarily parasites of rodents, chiefly rats and mice, though some have become adapted to pigs, cattle, or dogs. In many cases the micro-organisms are so well adapted to their normal hosts that they establish large colonies in the tubules of the kidneys, and exist there as commensals without apparently producing any deleterious effect on the animal host.

Intermittently some of the leptospires pass down the kidney tubules and are shed with the urine. If they reach water which provides suitable conditions the organisms can survive for days or even weeks. They enter new hosts either through broken skin or mucous surfaces, and so the cycle continues.

If the new host happens to be man or a susceptible domestic animal, pathological effects are produced and disease results. Although this is an accidental occurrence, it is one with important consequences from the human standpoint, and most investigators have directed their attention to the effects which follow infection of these casual hosts. There is evidence, however, which is put forward later, that fuller studies of the metabolism of the leptospire, and of the ecology of its natural hosts, might yield information of great value in the prevention of leptospirosis.

The first pathogenic leptospire to be isolated from man was the causal organism of Weil's disease. The discovery was reported in Japanese by Inada and Ido during February, 1915, and the micro-organism was named by them *Spirochaeta icterohaemorrhagiae*. A full record of these investigations was made in English by Inada, Ido, Hoki, Kaneko, and Ito (1916). Noguchi (1917) considered the morphology of this organism to be sufficiently characteristic to warrant the creation of a new genus, which he named *Leptospira*.

[*At this period the lecturer dealt with the classification and description of different species of Leptospira.*]

*The Milroy Lectures (abridged), delivered to the Royal College of Physicians on February 13 and 15, 1951.

In Table I are set forth the names and certain other characteristics of the species to which frequent reference will be made. The table also serves to illustrate how widely some species are distributed as compared with others.

TABLE I.—*Species of Leptospires*

Species	Carrier	Disease	Distribution
L. icterohaemorrhagiae	*Rattus norvegicus* (sewer rat). Other rats, and mice	Weil's disease; infectious jaundice	Almost world-wide
L. canicola ..	Dog	Canicola fever	Almost world-wide
L. grippotyphosa	*Microtus arvalus* (field vole)	Harvest, mud, field fever	Europe, Asia
L. pomona ..	Pig	Swineherd's disease	Europe, Asia, America, Australia
L. sejroe ..	*Mus spicilegus* (gleaner mouse)	Sejroe fever	Denmark, Central Europe
L. saxkoebing	*Apodemus flavicollis* (harvest mouse)	—	Denmark
L. bataviae	*R. norvegicus*	Indonesian Weil's disease	Indonesia
	A. sylvaticus (long-tailed field mouse)	Ricefield fever	Central Europe

There are equally marked differences in the number of species found in any particular locality. Collier (1948) states that 18 antigenically distinct species have been isolated in the Netherlands Indies. In Australia, five species are known to cause disease in man (Johnson, 1950). A large variety of serological types were isolated in the Belgian Congo by van Riel (1946). He did not regard their antigenic constitution as distinctive enough to warrant the establishment of separate species, and their relationships remain to be fully worked out and compared with known species.

In Central Europe, human infections have been reported with nine separate species. In addition to those shown in Table I there are *L. mitis*, a species which was first discovered in Australia by Johnson (1942), and *L. ballum* (Borg Petersen, 1944). Only one human infection with *L. ballum* has been reported (Borst, Ruys, and Wolff, 1948).

All cases of leptospirosis so far recognized in this country have been due to *L. icterohaemorrhagiae* and *L. canicola*. We have therefore tried to obtain information about the presence of other species by seeking evidence of human infections. Meningitis is one of the outstanding symptoms of the disease which these species produce in man, so we have tested serum from cases of meningitis for the presence of leptospiral antibodies. Through the kindness of Dr. F. O. MacCallum, of the Virus Reference Laboratory, London, we have been

able to examine serum from 642 cases of aseptic meningitis. The sera had previously been tested to exclude viral infections.

L. bataviae, L. grippotyphosa, L. pomona, and L. sejroe were chosen as a representative series, and the agglutination reactions of the sera were tested against these species, as well as against the two indigenous ones. In not a single instance was there the slightest indication of infection with any of the "foreign" species, although 17 cases of the pure meningeal form of Weil's disease and 8 of canicola fever were brought to light.

These investigations are being continued, and rodent surveys will be made if opportunity affords. From the evidence at present available, however, it appears that if other species of leptospires do exist in England they seldom if ever produce recognizable disease in man.

Leptospirosis in Domestic Animals

A number of species of leptospires can attack domestic animals, and at least two—*L. canicola* and *L. pomona*—seem to have no rodent hosts, depending for their propagation on dogs and pigs respectively. In this country, as far back as 1925, Okell, Dalling, and Pugh found that *L. icterohaemorrhagiae* was the cause of "yellows" in dogs—a severe and often fatal illness characterized by jaundice and prostration. As this leptospire is carried by rats, the disease is found more often in kennels—among foxhounds, for example—than in dogs kept as domestic pets.

Sporadic cases of jaundice, and also small but severe epidemics, in cattle and in pigs have also been traced to infection with *L. icterohaemorrhagiae* by Field (1949) and Field and Sellers (1950 ; 1951).

However, the most widespread disease of domestic animals is canicola fever in dogs. *L. canicola* is nearly as ubiquitous as *L. icterohaemorrhagiae,* and surveys in Scotland by Stuart (1946) and in England by Broom and MacIntyre (1948) have shown that from 25 to 40% of dogs become infected at some period during their lifetime. In typical cases the disease presents the symptoms of acute interstitial nephritis, and if the dog recovers it continues to excrete leptospires for some months at least, and probably a great deal longer. For as long as dogs continue to excrete leptospires they remain a potential source of danger to other dogs, and also to humans—because *L. canicola* is also pathogenic for man. In addition to these acute cases, many dogs become infected, and act as carriers, without presenting any signs of illness at all.

Leptospirosis in Man

The best-known and the most widely distributed form of the human disease is of course leptospirosis icterohaemorrhagica. It was also the first variety to be recognized as a clinical entity, though when Goldschmidt (1887) applied the term "Weil's disease" to the syndrome portrayed by Weil (1886) the aetiology was quite unknown. As noted above, *L. icterohaemorrhagiae* was not isolated until 30 years later, by Inada and his colleagues in Japan in 1915.

Weil's Disease

Since the middle of 1947 we have acted as the Leptospira Reference Laboratory for the Public Health Laboratory Service covering England and Wales, and in consequence we have an almost complete record of all the cases of leptospirosis which have been recognized in these countries during the past few years.

Within the period under review 465 cases of Weil's disease have been diagnosed in England, Wales, and Northern Ireland. In addition, there were 70 human cases of canicola fever in the two former countries. No case of the latter form of leptospirosis has yet been reported from any part of Ireland, although a survey we made of dogs in Dublin showed the canine infection rate there to be as high as it is in England.

The present series of cases of Weil's disease shows certain marked differences from an earlier one (Broom and Alston, 1948) which covered the years from 1940 to 1946. The death rate, which was 22% among the earlier cases, has now dropped to 15%, and the proportion of patients with jaundice has fallen from 90% to 74%. These two findings are in all probability closely related, for it is generally agreed that the death rate is negligible in non-icteric cases. We know of only one death without jaundice, and, so far as we are aware, no others have been reported in the literature. The importance of distinguishing between the icteric and non-icteric forms of Weil's disease will be apparent when the value of penicillin in treatment is under consideration later.

TABLE II.—*Weil's Disease: Age Incidence, Recoveries, and Deaths*

	Age in Years					Total	Age Unknown
	Up to 15	16–30	31–45	46–60	Over 60		
Recoveries ..	35	97	78	67	17	294	7
Deaths	0	3	24	23	7	57	1
Outcome unknown	1	2	4	3	0	10	49
Total cases ..	36	102	106	93	24	361	57
Case mortality ..	0	3	24	25	29	16	—

Age Incidence and Death Rate.—The age incidence and the death rates at different ages are shown in Table II. The low mortality figure for patients under 30 is in marked contrast to the heavy death roll in the later age groups. The data have been analysed in a number of ways, but no indication has been found that factors other than age had any special significance.

Sex Incidence.—In this series there were 26 females and 439 males. The high preponderance of men (95%) is the usual finding, except among fish-cleaners, an occupation in which most of the workers are women. When the chance of infection is the same there is no difference in the incidence between the two sexes.

Seasonal Incidence of Weil's Disease

Fig. 1 shows diagrammatically the monthly incidence of Weil's disease. The monthly totals in each case have been expressed as a percentage of the corresponding totals for the whole period, and the ordinate scale in the upper diagram has been reduced to one-half of that used for the other two. These expedients were adopted for ease of visual comparison, and the appropriate totals are inserted in each chart. In carrying out this analysis, the cases were allocated to the various months according to the date of the onset of symptoms. The actual infection must have occurred from one to two weeks earlier, but the length of the incubation period is seldom known with any degree of accuracy. On the other hand, the date of onset is easily determined, and has been used for that reason.

The incidence of bathing infections is represented in the upper histogram and, as is to be expected, a strongly

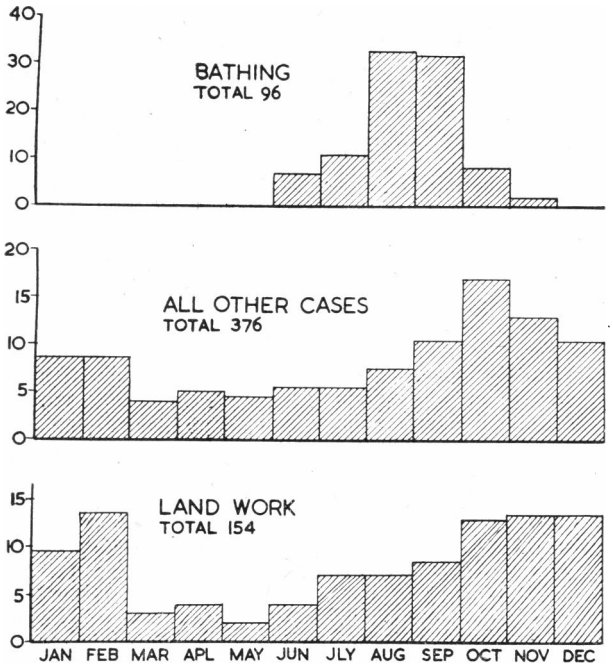

FIG. 1.—Percentage monthly incidence of Weil's disease.

marked seasonal influence is apparent. The first cases appear in June, and two-thirds of the total occurred during August and September.

All cases, except those due to bathing, are included in the middle histogram. The seasonal variation is much less obvious in this instance, but there is a decided tendency for the numbers to increase in the late summer and autumn, and to fall to a minimum during spring and early summer. The reason for this rhythm is unknown, but it may be one of the matters on which light would be cast by a study of the ecology of the rodent carriers, and of the metabolism of the leptospires.

The incidence among agricultural workers has been charted separately, for a reason explained later, although these cases are included in the centre histogram also. It will be noted that the autumnal rise in incidence is maintained throughout the winter, and that the infection rate remains low during spring and early summer. It may perhaps be conjectured that the rat population around farmyards and buildings rises when the harvest has been brought in from the fields. Certainly large numbers of rats are disturbed and killed when threshing operations are in progress, and the chances of contamination with infective urine must be very high at these times. We heard recently, for instance, of a farm on which no fewer than 600 rats were destroyed during the threshing of a single stack of grain.

Occupational Incidence of Weil's Disease

In Table III is set out the manner in which infection was contracted, so far as it was related to occupation or avocation. The most striking feature is the very high place occupied by agricultural workers, who constitute nearly one-third of the total number of cases. On the other hand, sewer-workers and coal-miners, whose work is recognized as carrying a special risk of infection, contribute together rather less than one-half as many cases as resulted from bathing.

It should be noted that persons handling food provide as many cases as do coal-miners. This category includes butchers, but for the most part the patients were employed in establishments where food was prepared for human consumption. It therefore seems that the level of hygiene in a number of such places still leaves much to be desired.

The "miscellaneous" group contains a few cases in which no obvious source of infection could be traced, but as a rule the possibility of contact with rat urine was quite clear. For example, some of the patients were rat-catchers, or men who had handled or had been bitten by rats; some were artisans whose work took them into rat-infested buildings; some lived in rat-ridden houses; and some had run the risk of infection in various ways, perhaps on a single occasion only.

TABLE III.—*Occupational Incidence of Weil's Disease, 1947–50 (418 Cases)*

	%
Farm-workers	31
Bathing and accidental immersion	19
Sewer-workers	5
Coal-miners	4
Handlers of food	4
Fish-workers	3·5
Working in water	2·5
Miscellaneous	31

Agriculture

The association between work on the land and certain forms of leptospirosis is of course well known. One may cite, for instance, canefield fever in sugar-cane workers in Queensland, Australia (Johnson, 1950); sejroe fever in harvesters in Denmark (Borg Petersen, 1949); the many epidemics of mud-fever (Kathe, 1950); and *L. bataviae* infections in the rice fields of Italy (Mino, 1938). A high incidence of true Weil's disease in agricultural workers in Japan was noted by Tohyama (1924), but the frequency of its occurrence in land-workers in other countries is not perhaps always appreciated—indeed, it is not even mentioned by Walch-Sorgdrager (1939) in her very extensive monograph on leptospirosis.

However, over 30% of the patients in this present series were engaged in agricultural work. Over the past 15 years there has been an increase both in the number of cases in farm-workers and in the fraction which they constitute of the total of all cases. It is difficult to decide whether this

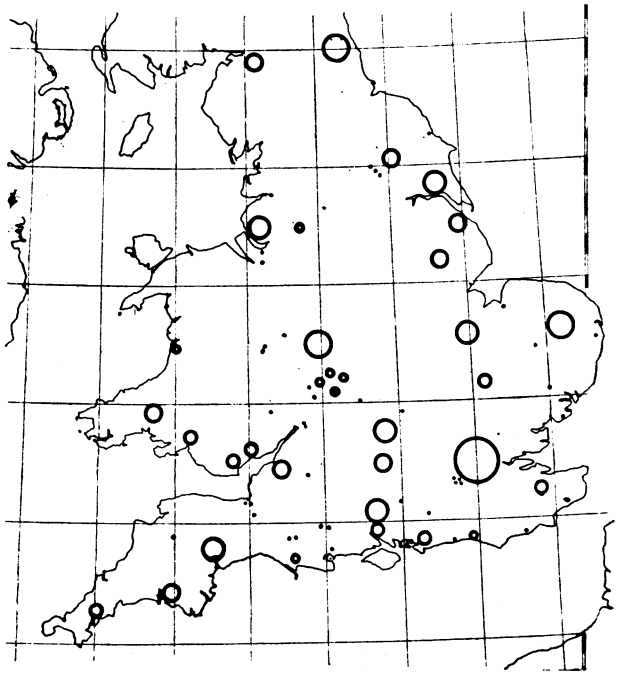

FIG. 2.—Map showing distribution of Weil's disease, 1947–50.

is the result of improved diagnostic facilities or whether it represents a true rise in incidence in agricultural districts.

In this connexion it is interesting to note that Adam (1950), who analysed the distribution of Weil's disease in North Germany, found the disease to be limited, in the main, to the lower reaches and the estuaries of the great rivers and their tributaries. In purely rural areas, away from the rivers, the incidence was low. Fig. 2 shows the distribution of cases of Weil's disease in England and Wales during the last few years. The size of the circles indicates approximately the relative numbers reported from the different areas.

In this country, of course, there is no wide hinterland, far removed from river estuaries, but the diagram suggests that there is a tendency for cases to cluster about the mouths of rivers and along their courses. In the valley of the

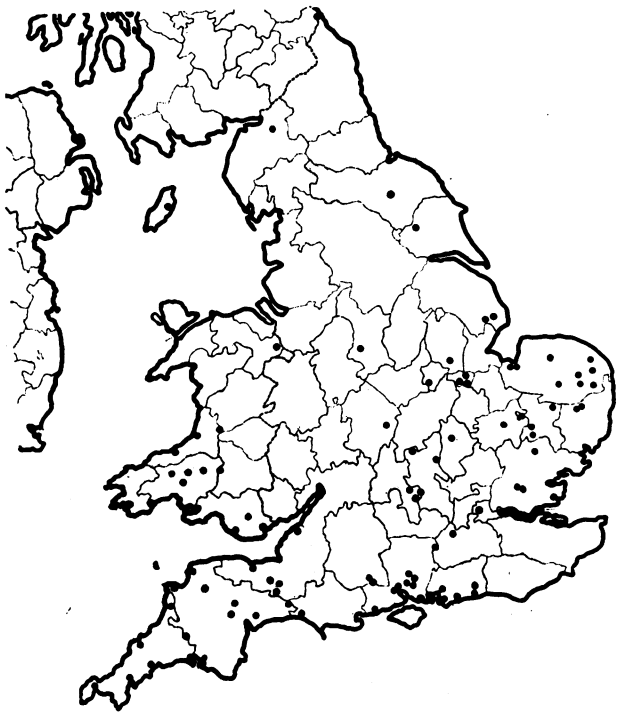

FIG. 3.—Map showing areas where Weil's disease occurred in farm-workers, 1947–50.

Thames, for example, there have been many cases around London, Reading, and Oxford. Other groups of cases occur along the courses of the Severn, the Test, the Humber, and the many rivers of East Anglia.

In Fig. 2 it was not feasible, because of the numbers involved, to plot the towns and villages in which each case occurred, but that discrimination has been made for infections among agricultural workers in Fig. 3. It will be seen that many cases occurred in East Anglia, in South-western England, and in Wales. There is less inward spread from the coast in the more northerly centres of infection, but the disparity may be the result of differences in the distribution of good agricultural land in divers parts of the country. A series of observations, taken over a number of years, will be required to show whether the infection is gradually infiltrating from the coastal areas along the lines of the rivers. Useful information could perhaps also be obtained by making surveys of the infection rate in rats, trapped in different parts of the country, over a period of years.

Coal-mining

Coal-mining has long been recognized as an occupation carrying a high hazard of infection with Weil's disease.

In contrast to the high incidence recorded in this country in the past, the total number of cases reported during the past four years for the whole of England and Wales was only 15. From our inquiries it appears that three factors are responsible for the reduced incidence. These are increased mechanization, improved methods of water-pumping, and the closing of a number of "drift" mines.

Mechanization involves the introduction of conveyer-belts to take the place of ponies or horses. This change drastically curtails the potential food supply of rats, and thereby leads to a decrease in their numbers. Better pumping reduces the proportion of wet mines, which provide suitable conditions for the survival of leptospires shed in rat urine. Drift mines—also known as slant or slope mines—lie comparatively near the surface, and a roadway leads in a horizontal or inclined direction from the surface to the workings. Mines of this type are well suited for horse-haulage; they are particularly apt to become damp, because of seepage of water from the surface: and they provide easy access for rats. Jenkins and Sharp (1946) found that the risk of infection in these mines was very much greater than in deep pits served by vertical shafts.

The combined effect of these changes, in addition to rat-destruction and improvement of personal hygiene among the workers, seems to have led to a very distinct reduction in the risk of infection in coal-mines.

Sewers

The relative incidence among sewer-workers is probably much higher than among coal-miners, for Alston and Brown (1935) found leptospiral antibodies in 9 of 45 London sewer-workers, although none of them had suffered from clinical Weil's disease. In a similar examination of healthy sewer-workers in another part of London we recently found agglutinins for *L. icterohaemorrhagiae* in 3 out of 18. These also must have been the result of subclinical infections, but the large number of positive reactors indicates that the men must often come in contact with the organism.

An interesting variation in incidence among London sewer-workers occurred between 1939 and 1950. The number of cases fell sharply in 1940, and remained at a low level throughout the period of the war, but during the past few years there has again been an increase. The most likely explanation was the cessation, during the war, of any extensive repairs and renewals of sewers. This work involves the removal and replacement of brickwork and concrete, and men engaged in these tasks are prone to suffer skin abrasions. They are therefore more liable to contract the disease than "flushers," whose duties entail less manual labour.

Intensive measures for the destruction of rats were of course undertaken during the war, but were not put into force till late in 1942, and so could have played no part in the early fall in incidence. It is very regrettable that work in sewers still carries a comparatively high hazard of infection, but we may hope that the continuous campaign against rats, and also the improvement in methods of personal protection for the workers, will mitigate, if they cannot entirely eliminate, the risk.

Bathing

The risk of contracting Weil's disease while bathing in canals, rivers, and stagnant pools is well illustrated, since bathing provided the second highest total of cases. The effect of weather conditions was very marked in the hot summer of 1949, when 33 cases were reported in contrast to 15 in 1948 and 16 in 1950.

Canicola Fever

The symptoms of classical Weil's disease are too well known to need recapitulation, but the so-called "benign form," which is indistinguishable clinically from canicola fever, has received much less attention in this country. In these cases meningitis is often the outstanding feature, and the possibility of leptospirosis may never be considered in the differential diagnosis.

Clinical Aspects

Canicola fever may be taken as an example of the benign form. Table IV shows the relative frequency of various symptoms, as observed in 54 of the cases which occurred in England and Wales in the past three years. To facilitate comparison the frequencies are expressed as percentages. Since complete details are not available for every case, the totals are not all identical, and absolute numbers would give a misleading impression.

[*At this point the lecturer dealt with the symptoms and complications of canicola fever, laying particular stress on the frequency of eye affections.*]

TABLE IV.—*Symptoms in 54 Human Cases of Canicola Fever*

Symptom	%	Symptom	%
Headache	90	Albumin in urine	43
Meningitis	78	Casts in urine	14
Stiffness of neck	78	Rash	20
Injection of eyes	58	Jaundice	18
Muscle tenderness	58	Haemorrhages	16

Complete recovery is the rule, but one fatality occurred in our series, and has been fully reported (Weetch, Colquhoun, and Broom, 1949). The patient had suffered for many years from chronic nephritis, and the damaged kidneys were unable to meet the additional strain.

Only one other death from canicola fever has been recorded—in Holland (Wolff, van Dam, and Minkenhof, 1951)—and in this case also the patient was suffering from a long-standing lesion of the kidney. To avoid confusion it should be noted that the reference quoted is the first published account of the Dutch case. It was, however, mentioned by van Thiel (1948) as "the first fatal case in the Netherlands, observed by Ruys in 1947," and also by Weetch *et al.*, who give the reference as "Ruys (1947)," and state in a footnote that information about the patient had been supplied in a personal communication from Professor Charlotte Ruys and Professor Wolff.

Sex and Age Incidence

Dogs are the carriers of *L. canicola*, so the disease is a domestic rather than an occupational one. For that reason the epidemiology of canicola fever differs in many respects from Weil's disease. In this series the sex distribution was 44 males and 26 females; this is about 63% of males, as compared with 95% in Weil's disease.

The age distribution of 64 cases of canicola fever is shown in Table V, in the same age-periods as were used in Table II for Weil's disease. It will be noted that the highest incidence is among adults, as in Weil's disease. When one considers the very intimate association that often exists between dogs and small children it may seem surprising that the incidence is not much greater in the youngest age group, whereas in fact only one of our patients was under 5 years of age.

TABLE V.—*Canicola Fever: Age Incidence*

	Age in Years				Total
	Up to 15	16–30	31–45	46–60	
No. of cases ..	15	21	21	7	64

From inquiries into the history of our cases it seems clear that the infectivity of *L. canicola* must be low for humans. It is usual to find that only those persons in a household who have nursed a sick dog and cleaned up its dejecta have contracted the disease. We have been able to examine samples of serum from all the members of a few families in which a single human case has occurred and where the source of infection was proved to be a pet dog that had recently been ill. In all these instances the sera, except of course the patient's, gave completely negative reactions. From this it appears that close contact with infective material is an essential factor in the transmission to man.

Multiple cases did occur in some households, but it is our experience that this happens only when two or more persons share the duties of cleaning up the infective urine passed either by a sick dog or by a healthy carrier. In a recent paper, Steigner and Messerschmidt (1950) report exactly similar findings in comparable investigations.

The disease can also be contracted by bathing in contaminated water, and this appeared to be the most likely source of infection in a small number of our patients. For instance, one boy, shortly before he fell ill, had been bathing in a pool in which the carcass of a dead dog was floating.

There still remains, however, a proportion of cases in which neither the likely source of infection nor the method of transmission was discovered. Much further work will be required before all the responsible epidemiological factors are elucidated.

Seasonal Incidence

Fig 4, which has been prepared in the same way as Fig. 1, shows the monthly incidence of human cases in the upper histogram. The numbers are too small to

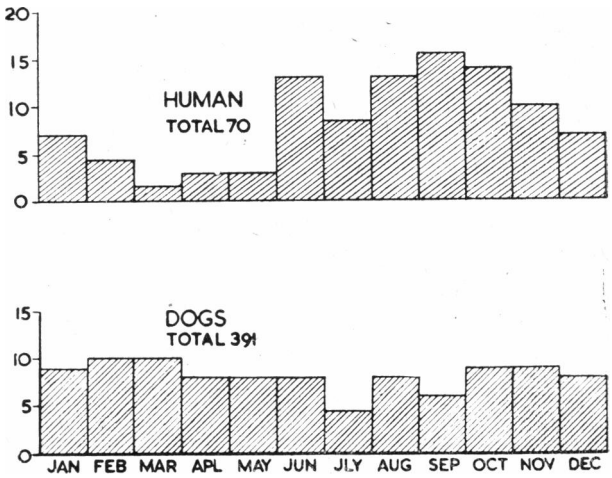

FIG. 4.—Percentage monthly incidence of canicola fever.

permit any definite conclusions to be drawn, but there seems to be a tendency for infections to occur more often in the second half of the year.

The incidence in dogs, represented in the lower histogram, seems to be unaffected by season. This finding differs from the opinion, held by most veterinary practitioners, that canicola fever is essentially a winter disease. That view seemed to be supported by our earlier observations (Joshua and Broom, 1949), but the results obtained then have not been confirmed as the scope of the investigations widened.

Laboratory Diagnosis

The early stages of leptospiral meningitis may simulate meningitis of tuberculous or viral origin, and a tentative diagnosis of one of these conditions is often made. It is possible that estimations of the erythrocyte sedimentation rate and the glucose content of the cerebrospinal fluid may help to discriminate among these conditions.

Erythrocyte Sedimentation Rate

Emphasis has been laid recently on the marked increase which takes place in the E.S.R. during the early stages of leptospirosis by a number of German writers (Krämer and Wieland, 1949 ; Scheid, 1949 ; Glattkowski, 1950 ; Litzner and Hahn, 1950 ; Stahl and Tetzner, 1950). From their investigations of an epidemic of field-fever Litzner and Hahn concluded that the raised E.S.R. is a constant and characteristic finding. They go so far as to say that a normal E.S.R. would in their opinion rule out a diagnosis of leptospirosis. These workers also state that the E.S.R. is normal in patients suffering from aseptic meningitis, so that this test is of diagnostic value.

Glucose Concentration in Cerebrospinal Fluid

Rubie and Mohun (1949) examined cerebrospinal fluid from a series of cases of tuberculous meningitis and found the sugar concentration to vary between 5 mg. and 45 mg. per 100 ml. The observations in leptospirosis again come almost entirely from German workers, who state that concentrations above 50 mg. are the rule. For example, Glattkowski (1950) gives details of 13 cases of canicola fever. In one patient the glucose content, which was 60 mg. per 100 ml. on the second day of disease, fell to 32 mg. on the fourth day. All the other cases showed levels of 50 mg. or more, up to the end of the second week, and nine had concentrations above 80 mg. per 100 ml.

In the past we have not, as a rule, investigated the exact concentrations of glucose, but we have a certain number of such records. In some instances the levels were above 50 mg. per 100 ml., but in others they were below that figure, and in one case the concentration was only 18 mg. per 100 ml. It appears, therefore, that a high sugar content is not an invariable finding, but if the estimation makes it possible to exclude tuberculosis meningitis in even a proportion of cases it is obviously a useful examination to carry out.

Much more work will be required to confirm these observations before they can be accepted as reliable aids to diagnosis, but they have at least the advantage of simplicity, and certainly merit full investigation.

Histological Examinations

An aid to the early diagnosis of Weil's disease might perhaps be found in the examination of biopsy specimens of muscle or of liver tissue.

Muscle Biopsy.—As long ago as 1916, Beitzke gave a good description of the degenerative changes which are found in voluntary muscles—especially the gastrocnemius. The condition affects single muscle fibres or small groups of adjacent fibres. The cytoplasm of the fibre loses its cellular detail, the striations disappear, and only fragmented masses of hyaline material remain. The adjacent unaffected portions of the fibre show no apparent alteration, and there is little or no inflammatory reaction. Sheldon (1945) carried out a series of biopsies at different stages throughout the acute attack and during convalescence, and he found that if the patient survives the fibres regenerate as a rule without fibrosis. Gardner and Wylie (1946) examined biopsy material from one patient suspected to be suffering from Weil's disease. They found the characteristic changes present some days before the agglutination test gave even an indefinite positive reaction. So far as we know, this method has not been used by any other workers up to the present.

Liver Biopsy.—In many fatal cases of Weil's disease the histological appearance of the liver seems compatible with life. Himsworth (1947) said that the essential character of the lesion will never be fully understood until a series of observations is made on biopsy material taken at different stages of the disease. Most workers have considered that the haemorrhagic tendency present in Weil's disease presents too great a hazard to the patient to justify the use of this type of investigation. Ostertag (1950), however, carried out liver biopsy in a series of 11 cases. He states that no special precautions were taken, and that no untoward incidents occurred as a result of the procedure. He found that the characteristic disorganization of the cord system and also signs of regeneration were present at an early stage, even before the appearance of jaundice.

These investigations are suggested as an aid to the early diagnosis of leptospirosis, but they cannot of course discriminate among the forms caused by different species. This can be done by isolating the strain from the blood during the first week of illness, or from the urine, where it appears towards the end of the second week. The isolation may be made by direct culture, or by the inoculation of susceptible animals and subsequent culture. In either case the identification is completed by serological tests. Alternatively, the patient's serum can be tested for the presence of leptospiral agglutinins, and the infecting species determined in this way.

Neither of these methods will provide an early diagnosis. As a rule antibodies cannot be demonstrated before the end of the first week, and in a few of our cases production was delayed for more than three weeks. It is true that leptospires can be found in the blood in the earliest stages, but five days or more must elapse before visible growth appears in cultures or, in the case of animal inoculation, before pathological effects are produced.

Thus, although these are the only two methods which provide unequivocal results, their value lies in confirming a clinical diagnosis rather than in furnishing evidence on which a diagnosis may be based or a line of treatment be indicated. It is for the latter purpose that the other techniques have been dealt with more fully, and in no wise because it is considered that they could ever supersede the well-established serological methods.

Treatment

The therapeutic use of antileptospiral serum in Weil's disease is well known, and is of proved value if treatment is begun within the first five days of illness. Early diagnosis is, however, the exception rather than the rule, unless the patient's occupation carries a known risk of infection, so most of the records refer to sewer-workers, coal-miners, or fish-cleaners.

Penicillin

Until penicillin became available none of the drugs used in the treatment of acute febrile illnesses had any curative effect in Weil's disease, although many remedies had been advocated from time to time. In animal experiments it was shown by Heilman and Herrell (1944) and by Alston and Broom (1944) that this antibiotic could prevent the appearance of symptoms in guinea-pigs, provided that treatment was begun within 24 hours of infection with *L. icterohaemorrhagiae*. These observers, however, and also Augustine, Weinman, and McAllister (1944), found the drug completely inactive if it was withheld until the animals showed signs of illness. On the other hand, Borg Petersen and Schmidt (1945) were able to cure the disease in guinea-pigs even when treatment was not begun until the fourth day after infection, and by that time the animals were manifestly sick.

Reports on the action of penicillin in human cases of Weil's disease are nevertheless often favourable. In many instances, however, this conclusion has been reached from the results in a single case or a few cases. Not infrequently, also, the drug was first administered at a comparatively late stage of illness, by which time the outcome of the attack has already been determined by the extent of the kidney damage, unless other lines of treatment are adopted.

Of those observers who have treated a number of cases, Bulmer (1945) was dealing with soldiers who contracted the disease during the summer of 1944. He states than 39 cases of Weil's disease were diagnosed, but he gives no details of the number treated with penicillin or of the results obtained. He formed the impression, however, that the antibiotic had a useful therapeutic action. On the other hand, Smith (1949), from the experience of 16 cases, thought that penicillin had little effect in toxic patients.

As compared with these small numbers, we have records of 206 cases of Weil's disease treated with penicillin in a number of hospitals in Britain during the years 1947–50 inclusive. Details of dosage and of the day of disease on which treatment was begun are, however, available for a minority only. Thirty-four of these patients died. This represents a case mortality of approximately 17%, whereas the rate for the whole series was 15%. From the crude figures it thus appears that penicillin therapy does not improve the prognosis of Weil's disease.

To compare these results with the position before penicillin was available the series reported by Broom and Alston (1948) may be used. None of the patients in the latter series received penicillin, and the death rate was 22%. It must be noted, however, that the proportion of non-icteric cases was also much lower, and, as noted above, death is very rare in the absence of jaundice. It therefore seemed that a fairer comparison would be the death rates among jaundiced

TABLE VI.—*Weil's Disease: Death Rates for Jaundiced Cases*

Description	No. of Cases	Deaths
Cases in 1947–50	263	54 (20%)
Cases treated with penicillin ..	152	34 (22%)
Cases in 1940–6	103	24 (23%)

patients. Table VI shows that the corrected case mortality for the earlier series now becomes 23%. For all jaundiced cases in the present series the rate is 20%, and for those treated with penicillin it is 22%. When the crude statistics are corrected in this manner there is still no indication of any benefit from treatment with penicillin.

These results may be analysed in another way. From the animal experiments it was evident that the curative effect of penicillin was greatest when the drug was given during the first days of illness. Suchett-Kaye (1951), recording the successful treatment with penicillin of six consecutive cases, stresses the importance of the early institution of antibiotic therapy.

We have records of 51 cases in which the day of disease on which treatment was begun is known, and the results are shown in Table VII. Thirty-six patients recovered, and for the last line of the table the number of recoveries which would be expected in each period if the drug had no beneficial action has been calculated. The probability (P) that the differences could be the

TABLE VII.—*Weil's Disease: Penicillin at Different Stages*

	Interval in Days from Onset to Treatment				Total
	1–5	6–10	11–15	Over 15	
Deaths	2	11	2	0	15
Recoveries ..	8	19	5	4	36
Recoveries expected	7·0	21·2	7·8		36

P = 0·8

result of chance is 0.8, which means that a difference as great or greater than this would be expected 8 times in 10 trials.

The conclusion must be drawn, therefore, that these patients at least obtained no benefit from the administration of penicillin at any stage of the disease.

If the general case mortality of 20% is applied to the series reported by Suchett-Kaye, a similar calculation shows that the recovery of every patient in a set of six consecutive cases could be expected to occur in approximately 5 out of 10 such sets as the result of chance alone if the treatment had no effect whatsoever.

An interesting parallel to these findings is shown by the action of penicillin in dogs infected with *L. icterohaemorrhagiae*. Joshua and Freak (1947) noted very little response to penicillin therapy, in contrast to the dramatic improvement effected by the drug in the early stages of canine canicola fever. The latter is not a fatal disease in man, so no similar comparison can be made for human infections.

In view of the results of this analysis, it is surprising to note that most clinicians report a marked improvement with penicillin treatment. Further investigations may show that in favourable cases the antibiotic speeds recovery and shortens the tedious convalescence which is so characteristic of leptospirosis.

Other Antibiotics

No report of the use of streptomycin in human leptospirosis has been published, although it was found effective in experimental infections of hamsters with *L. icterohaemorrhagiae* by Heilman, Knutson, and Greenburg (1945). In our series five patients received this drug, sometimes in conjunction with other antibiotics, and four recovered.

"Aureomycin" was used in three other cases, with two recoveries and one death. Two other patients were treated with chloramphenicol, and both died. No conclusions can be drawn from such a small number of cases, though favourable comments on the action of aureomycin have been made on the result in single cases by Lurie (1949), Brainerd *et al.* (1949), and Batchelor and Todd (1950).

Other Lines of Treatment

In fatal cases of leptospirosis death usually ensues about the 14th day, and is the result of uraemia following damage to the kidneys. The exact nature of the renal lesion is not fully understood, but it produces symptoms similar to those found in blackwater fever, incompatible blood transfusion, crush injuries, and traumatic uraemia following wounds by high explosive missiles, as described by Darmady *et al.* (1944). The kidneys in all these conditions present certain pathological features in common. The cortex is pale, and the medulla dark and engorged. Histologically the glomeruli appear relatively normal, but degenerative changes are widespread in the convoluted tubules and loops of Henle.

Darmady and his colleagues suggest that the renal failure may be due to anoxia of the kidney, possibly resulting from a period of hypotension or from neurogenic vascular disturbance. In blackwater fever, Maegraith and Findlay (1944) consider, to use their own words, "one of the more probable causes of renal failure is an alteration in the distribution of the blood flow through the kidney whereby circulation through the glomerular capillary beds is so reduced that filtration is grossly restricted." They think that the blood flow through the cortex has been mainly short-circuited into the medullary vessels, with some of the blood running direct through the cortex to the subcapsular vessels.

The renal circulation has been intensively studied by Trueta *et al.* (1947), and their investigations have shown the existence in rabbits of an alternative, intrarenal circulation through which the blood can by-pass the cortex. If such a mechanism is present in man it would offer a possible explanation of the renal failure in these conditions of such apparently varied aetiology.

Evidence in favour of this hypothesis is the re-establishment of renal function which follows paralysis of the sympathetic nerves. Robertson (1946) and Williams (1947) have successfully treated anuric cases of Weil's disease by high spinal anaesthesia, and this method has been found effective by other workers in anuria following incompatible blood transfusion. As Williams points out, it is necessary to raise and to maintain the blood pressure at a sufficiently high level to promote full urinary secretion.

Other means might be taken to tide the patient over the critical period of anuria, and to reduce the blood-urea level, until the kidneys resume their function, as they will do in time provided death can be averted. Peritoneal dialysis was used by Reid, Penfold, and Jones (1946) to relieve the uraemia in one patient suffering from anuria following incompatible blood transfusion; The artificial kidney was employed by Murray, Delorme, and Thomas (1949) in a similar case, and in two others in which uraemia followed acute sepsis.

These methods have not been tried in the treatment of Weil's disease, but exchange transfusion has been practised in one case. This technique had been carried out successfully by Dausset (1950) in 29 of 44 cases of anuria resulting either from sepsis or from the ingestion of various poisons, but it failed in this case of Weil's disease. The patient received 9 litres of blood in two days, and his condition improved for a time. Some four hours after the second transfusion, however, he collapsed suddenly, and died within a further two hours. The sudden and unexpected death was thought to be due to a transfusion incompatibility and not to the leptospiral infection.

From this rapid review it appears that these temporary expedients may sometimes at least be of great value. Reports about many more cases will, however, be required before the most effective method will emerge.

Prevention

Prophylactic measures may be designed (1) to provide personal protection; (2) to destroy leptospires; (3) to prevent contamination by carrier hosts.

Personal Protection

(*a*) *Serum.*—Injections of specific immune serum have been administered to laboratory workers who have been cut or scratched with instruments contaminated with infective material. This method has also proved effective in protecting valuable dogs which had been exposed to a high risk of infection with *L. icterohaemorrhagiae.* As a preventive measure it has, however, no general application.

(*b*) *Vaccines.*—The protection of large numbers of coal-miners in Japan against Weil's disease by the inoculation of culture vaccines of *L. icterohaemorrhagiae* was carried out by Wani (1933). Fairly severe local and general reactions were noted in a considerable proportion of the subjects, but Wani claimed that the case incidence among the vaccinated men was much lower than in control groups of unprotected miners. Smith (1937) used the method experimentally, but no other large-scale test has been made in man. A similar vaccine is extensively used for the prophylaxis of yellows in dogs, and more recently a vaccine of *L. canicola* has also been introduced. These vaccines have generally consisted of whole cultures in which the organisms were killed by phenol or formalin; but the method advocated for dogs by Meyer and Brunner (1950) of using washed suspensions of leptospires killed by freezing may provide a product which is less likely to cause severe reactions in man.

(*c*) *Protective Clothing.*—The wearing of rubber boots and gloves, which should be washed with disinfectant before being removed, would be likely to give a good measure of protection. This method would be practicable only when the number of persons at risk was small, and when work could be carried out while wearing heavy gloves. It could not be applied, for instance, in the circumstances of the epidemic of field-fever described by Popp (1950). That outbreak occurred among pea-harvesters, who are not regular agricultural workers. Some 10,000 persons were recruited annually in one district, and they were employed for a period of four to five weeks only.

(*d*) *Hygiene.*—In occupations which carry a known risk of infection, workers should clean and disinfect cuts and abrasions as soon as possible, and they should avoid practices, such as leaving scraps of food, likely to attract carrier rodents. Chang, Buckingham, and Taylor (1948) found that leptospires are rapidly killed by small concentrations of "halazone," a compound containing chlorine, and the use of a barrier cream containing this chemical has been suggested. We have carried out a few experiments with creams in which were incorporated various compounds which liberate chlorine in contact with water. The abdomen of guinea-pigs was shaved, and the skin lightly scarified. The cream was thoroughly applied over the whole area, and thereafter a single drop of a virulent culture of *L. icterohaemorrhagiae* was allowed to dry on the surface. In no case have the compounds so far tested prevented infection, but the work is being continued in the hope that an effective one may be found. By making widely known the risk of contracting Weil's disease by bathing in stagnant water, a considerable reduction in the number of cases should be achieved.

Destruction of Leptospires

Tohyama (1924) recommended the use of calcium cyanamide as a fertilizer to reduce the incidence of Weil's disease in the rice fields of Japan. The destructive effect of this material was considered by Taylor and Goyle (1931) to be due to the di-cyandiamide which it always contains, and the method would be applicable only in special circumstances.

Prevention of Contamination

(*a*) In the case of Weil's disease measures should be taken to make premises proof against rats, and continuous campaigns of rat-destruction should be carried out. Fresh-water bathing pools should also be protected, and the water chlorinated to destroy any leptospires which may gain access.

(*b*) Canicola fever presents a different problem because of the association between dogs and man. Owners of sick dogs should be warned of the chance of infection and advised to

disinfect the animal's dejecta. When a human case is diagnosed every effort should be made, by testing samples of serum in the presence of agglutinins, to trace the dog which provided the focus of infection. As has already been mentioned, it is important to bear in mind that dogs, including young untrained puppies, may be symptomless carriers.

According to Brunner and Meyer (1949), once leptospires have become established in the kidney tubules they cannot be eradicated by penicillin therapy but only by a course of treatment with streptomycin, in daily doses of 40 mg. per kg. of body weight for four days.

Summary

A short review is given of the history and classification of the genus *Leptospira*; of the distribution of different species; and of the diseases they produce in domestic animals.

An analysis of 465 cases of Weil's disease which occurred in England and Wales from 1947 to 1950 is made with regard to age, sex, occupational, and seasonal incidence, and also the incidence in different parts of the country.

Attention is drawn to the high incidence among agricultural workers and the number of infections contracted while bathing.

The suggestion is put forward that the reduced incidence in coal-miners may be due to a combination of increased mechanization, better pumping, closure of drift mines, and improved hygiene among the workers.

The symptoms most often noted in 54 cases of canicola fever are described, and some of the epidemiological differences between this infection and Weil's disease are enumerated.

The possibility is discussed of improving the early diagnosis of leptospirosis by estimating the erythrocyte sedimentation rate and the glucose concentration of the cerebrospinal fluid, and by the histological examination of biopsy material from liver and voluntary muscle.

An analysis is made of the results of treatment of 206 cases of Weil's disease with penicillin, from which it appears that the antibiotic does not reduce the death rate, irrespective of the stage of illness at which administration is begun.

A description is given of methods of prevention which are applicable in Weil's disease and canicola fever.

I should like to record my thanks to the many physicians and pathologists who have provided me with information and with material for investigation.

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Research in the U.S. army has developed a new foot powder to reduce foot perspiration by as much as 24%, thus offering partial protection against cold injuries to troops living or fighting in cold weather areas. The new preparation has a powdered talc base and contains aluminium chloride and potassium alum, as anhidrotic agents, as well as boric acid, salicylic acid, and starch, and the first shipment of the powder will be issued this autumn to troops assigned in cold weather areas, including those in Korea. The powder will be packaged in seven separate envelopes contained in one heat-sealed cellulose kit. This is a soldier's one-week supply. Troops will be instructed in its use. Additional research, using a combination of a rubber-barrier sock and the new foot powder, has shown a 60% reduction in perspiration. A new type rubber boot is being developed that will embody the principle of the rubber-barrier sock to eliminate the extra rubber-type sock. It will be used in combination with the foot powder. The powder is intended to be used alone where the military situation permits a daily change of socks and shoes. The secretion of the sweat glands is especially harmful in cold weather because crystallized particles of perspiration act as conductors of cold, thereby diminishing the insulative value of winter footwear. By reducing foot sweating, the new powder will decrease the risk of frost-bite —the danger of "dry-cold," just as trench-foot is the danger of "wet-cold."