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REFERENCES

- Anton-Stephens, D. (1954). *J. ment Sci.*, **100**, 543.
Board of Control Report (1954). Annual Report, 1953. London.
Elkes, J., and Elkes, C. (1954). *British Medical Journal*, **2**, 560.
Ey, H., and Berard, E. (1952). *Evolut. psychiat.*, **23**, 661.
Garmany, G., May, A. R., and Folkson, A. (1954). *British Medical Journal*, **2**, 439.
Howell, T. H., Pinner-Harsh, J. A., and Dietrich, M. (1954). *Practitioner*, **173**, 172.
Sigwald, J., and Bouttier, D. (1953). *Ann. Méd.*, **54**, 150.

L. CANICOLA INFECTION TREATED BY PENICILLIN

BY

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Human infection with *Leptospira canicola* is infrequently recorded in this country although the organism is widely distributed in the canine population. Thus Stuart (1946) has shown that 25 to 40% of dogs in Glasgow are infected with the organism, and Broom and MacIntyre (1948) found similar figures in London. In dogs the organism produces a pyelonephritis, following which the animals may excrete the organisms in the urine for several months (Stuart, 1946).

The literature has been admirably reviewed by Broom (1951). He believes the infectivity to be low, since it is usual to find that only those in a household who have nursed an infected dog and who have cleaned up its dejecta are liable to contract the disease. Although the routes of infection are not known with certainty, the entry would appear to be through intact or broken skin, mucous membranes of the upper respiratory tract, or the conjunctivae. Bathing in contaminated water is a not uncommonly reported mode of infection.

The clinical features are those of an influenza-like illness of sudden onset, with signs of meningeal irritation appearing early in the illness in about two-thirds of cases (Alston, 1949).

We report two further cases arising in Glasgow. One of these was a laboratory infection, and it was possible to estimate the incubation period. Both were successfully treated with penicillin.

Case 1

Five days before admission to hospital a housewife aged 52 was suddenly taken ill with severe pains in the legs and paraesthesia from the knees to the ankles. On the second day of the illness she began to complain of severe throbbing frontal headache and pain in the neck. On the following day the pains and paraesthesia in her legs disappeared and were replaced by severe backache. On the fourth day of the illness persistent nausea, retching, and vomiting began, associated with an erythematous rash on her legs.

On admission to hospital she was found to be a flushed, rather drowsy woman with a pyrexia of 100° F. (37.8° C.). Discrete erythematous macules were present on the front of both legs, with a pin-point erythema over most of her

back. The edge of the liver was palpable, as was the tip of the spleen. Slight neck rigidity was demonstrable. There was no jaundice. The total white blood count was 12,500 per c.mm. (85% polymorphs, 8% lymphocytes, 4% monocytes, 2% eosinophils). The E.S.R. (Westergren) was 40 mm. in the first hour. The urine showed no abnormality.

On lumbar puncture clear fluid was obtained at a pressure of 180 mm. of water. A pleocytosis of 584 cells per c.mm. (86% lymphocytes, 9% monocytes, 5% polymorphs) was present. The chemistry of the fluid showed: protein, 45 mg. per 100 ml.; sugar, 67 mg. per 100 ml.; and chloride, 725 mg. per 100 ml. No organisms were found microscopically or on broth culture.

During the two weeks preceding her illness the patient had been nursing a sick dog, and in view of this the veterinary surgeon who had been treating the dog was consulted. He stated that the dog had been suffering from a renal infection, and, whilst he had no bacteriological evidence of *L. canicola* infection, he thought this a likely diagnosis in view of the frequency of such infection among dogs in Glasgow.

In the light of this opinion, a provisional diagnosis of "canicola fever" was made, and, after blood specimens had been obtained for diagnostic purposes, treatment was instituted with crystalline penicillin, given intramuscularly in doses of 250,000 units six-hourly. This was begun one hour after admission—that is, on the fifth day of illness—and continued until the fourteenth day.

Within 24 hours there was relief of symptoms, and, after 48 hours, apparent clinical cure (see Chart).

Temperature chart of Cases 1 and 2.

Bacteriology.—The organism was not obtained on blood culture using ordinary media nor on guinea-pig inoculation, but serological tests confirmed the diagnosis in both the patient (Table I) and her dog, the latter's serum agglutinating *L. canicola* to a titre greater than 1/30,000. The same tests made on members of the patient's household, who had been in contact with the dog, were negative.

The patient was dismissed symptom-free two weeks after admission. A lumbar puncture carried out just before discharge showed a clear fluid under a pressure of 50 mm. of

TABLE I.—Results of Serum Agglutination Tests in Two Cases of *Leptospirosis Canicularis*

Day of Disease:	Case 1					Case 2			
	5th	13th	23rd	50th	72nd	8th	19th	24th	44th
Reciprocals of titres with:									
<i>L. canicola</i>	0	1,000	10,000	1,000	1,000	Neg.	Neg.	1,000	1,000
<i>L. icterohaemorrhagiae</i>	0	0	10	0	0	„	„	100	30

water and containing 17 lymphocytes per c.mm. The chemistry of the fluid was normal. The patient showed no evidence of relapse after six months' observation.

Case 2

A lecturer in veterinary medicine aged 33 was suddenly taken ill with headache, shivering, and backache. On the second day of the illness the headache became much more severe and he vomited repeatedly. On this day he was seen at home by one of us, when the only findings were a pyrexia of 104° F. (40° C.), a tachycardia of 140 a minute, and some abdominal distension. There was no evidence of a meningeal reaction. He was treated expectantly with half-normal saline by mouth. On the third day of the illness he felt slightly better. The vomiting had stopped, though nausea, retching, and headache persisted. The temperature was now 102.6° F. (39.2° C.), but on the following morning the headache was again intense and retching severe. The temperature was now 104° F. (40° C.). The spleen was palpable three fingerbreadths below the left costal margin, and small pink macules 1 mm. in diameter were present on the skin of the abdomen. A specimen of blood was taken for broth culture. The white cell count was 7,400 per c.mm. (93% polymorphs, 6% lymphocytes, 1% monocytes). The urine contained albumin and a few erythrocytes. The E.S.R. (Westergren) was 40 mm. in the first hour.

At this point the patient was closely questioned about the possibility of having acquired any infection in the course of his work. He now remembered that seven days before the onset of the illness he had broken a tube containing a culture of *L. canicola* and in so doing had cut his finger. He had immediately washed the wound with a solution of penicillin.

It seemed probable that the patient was suffering from *L. canicola* infection, and after a further specimen of clotted blood had been removed for culture he was given one million units of crystalline penicillin intramuscularly. Two and a half hours after the injection he had a very severe reaction. He felt very ill, and on taking his temperature found it to be 104° F. (40° C.). Immediately afterwards a severe rigor occurred which lasted about eight minutes. He felt extremely weak and was unable to feel his own pulse. After an hour he began to feel better, and, whereas previously he had been extremely restless, he was now content to lie still. Five and a half hours after the first injection of penicillin he was given a second dose of one million units. By this time he felt better, though he still looked very ill and had a temperature of 105° F. (40.6° C.). Two and a half hours later there was a marked improvement in his condition. His temperature was now 99° F. (37.2° C.), and his headache less severe (see Chart).

By the following morning (fifth day of illness) his improvement was remarkable. He had slept soundly, his appetite had returned, and the headache was only slight. The temperature was normal and the urine contained only a faint trace of albumin. The spleen was still palpable three fingerbreadths below the left costal margin.

The patient then made an uninterrupted recovery, the headache vanishing after three more days and the spleen soon becoming impalpable. He had received one million units of penicillin three times daily from the fourth to the seventh day of illness inclusive and the same dose twice daily from the eighth to the tenth day.

Bacteriology.—No growth was obtained from the broth culture. The specimen of blood clot was inoculated on to special media, and after four days' incubation *L. canicola* was isolated. The findings of serological tests carried out are shown in Table I.

Discussion

Pyrexia of Unknown Origin and Lymphocytic Meningitis

The ubiquity of *L. canicola* in this country is such as to make infection with this organism a possibility in every case of obscure fever. The clinical features, apart from the high

proportion of cases of meningitis, are often indistinguishable from those of any septicaemia. The clue to the diagnosis lies in the history of contact with a sick dog.

That the leptospira may be the cause of a lymphocytic meningitis should also be borne in mind. Broom (1951) examined the sera of 642 cases of aseptic meningitis and found that 25 gave positive reactions for leptospirosis (17 *L. icterohaemorrhagiae*; 8 *L. canicola*). The report by the Virus Reference Laboratory, Colindale (1953), gives the following results of serological examination of cases of suspected virus infections of the central nervous system during 1949 and 1950.

Year	No. Tested	No. Positive for Leptospirosis	
1949	130	10 (7.7%)	} 18 (6 <i>L. icterohaemorrhagiae</i> , 12 <i>L. canicola</i>)
1950	196	8 (4.0%)	

This report suggests that increasing awareness of leptospirosis may be responsible for the lower figure of 1950, since sera were often sent direct to Dr. J. C. Broom and by-passed Colindale.

Minkenhof (1948), Broom (1951), and Joe and Sangster (1951) all emphasized the necessity for distinguishing between the meningitis of leptospirosis and that of non-paralytic poliomyelitis. Indeed, Alston (1949) reported that two-thirds of the cases of *L. canicola* infection in man showed signs of meningeal irritation. Broom and Joe and Sangster pointed out that a raised E.S.R., which is usual in leptospirosis, may be useful in excluding poliomyelitis where the sedimentation rate is usually normal. The raised E.S.R. in Case 1 illustrates this point.

Incubation Period

Kelser and Schoening (1948) showed that the incubation period of *L. canicola* infection in hamsters was 6–10 days. The incubation period has not, however, previously been accurately determined in man. The unique circumstances of the mode of infection in Case 2 would appear to place it at about seven days.

Treatment with Penicillin

The recorded cases of human infection with *L. canicola* between 1946 and 1951 which were treated with penicillin are enumerated in Table II. The results do not appear

TABLE II

Case No.	Author	Penicillin		Result		
		Days of Illness*	Daily Dose (Units)	Cure	Relapse	Failure
1	Rosenbaum (1946)	12–18	?	—	—	No significant effect
2	Baber and Stuart (1946)	6–9	60,000	—	68th day	—
3	Laurent <i>et al.</i> (1948)	6–10	600,000	—	16th day	—
4	" "	4–7	600,000	Alleviation of symptoms on 6th day	—	—
5	Weetch <i>et al.</i> (1949)	17–?	960,000	—	—	Patient died 24th day†
6	Mackay-Dick and Watts (1949)	8–15	2,300,000	—	17th day	—
7	" "	29–51	360,000	—	47th and 78th days	—
8	Campbell <i>et al.</i> (1950)	9–12	2,000,000	—	Recrudescence of fever during treatment	—
9	" "	4–14	200,000	—	—	—
10	" "	8–16	200,000	Claim only modification of course of disease	—	—
11	Joe and Sangster (1951)	7–?	?	—	—	No spectacular benefit
12	Fox and Fyfe (1951)	3–11	?	—	—	" — "
		6–19	300,000	—	24th day	—

* Days of illness are inclusive.

† Coincidental chronic nephritis.

encouraging. The difficulty in assessing the value of penicillin therapy is common to all conditions which tend to natural cure. It is especially difficult when different doses have been used and treatment has begun at different stages of the disease. In the case of *L. canicola* infections a further factor must be taken into account. McIntyre and Stuart (1949) have shown that in dogs there is an invasive or septicaemic stage followed by a later stage where there is renal involvement. Dogs in the first stage all recovered after penicillin treatment, but there was a 50% mortality if the kidneys were involved. The ineffectiveness of penicillin in the renal stage of the infection is further suggested by McIntyre and Montgomery (1952) and Brunner and Meyer (1949), who have shown that the organism can be recovered from the renal tubules 14 months to two years after treatment.

The very rapid response to penicillin in high dosage in our two cases strongly suggests a therapeutic effect. It is to be noted that both were treated early and were probably mainly in the septicaemic stage, although Case 2 showed some albuminuria. The severe reaction shown by Case 2 was of Herxheimer type, and is further evidence of a lethal effect on the organisms. It is perhaps significant that the only other recorded case of rapid improvement after treatment with penicillin (Case 4 in Table II) also received large doses early in the disease.

Stagg and Leibovitz (1951) believe that chlortetracycline ("aureomycin") is an effective therapeutic agent in *L. canicola* infection. The evidence for this is inconclusive, since in their case 18 hours of treatment with penicillin in high dosage had preceded chlortetracycline. In experimental *L. canicola* infection in hamsters, Heilman (1945) found that the protective effect of penicillin was greater than that of streptomycin.

Since no other satisfactory treatment is known, it seems desirable to treat recognized examples of this disease with large doses of penicillin as early as possible after infection.

Summary

Two cases of human infection with *Leptospira canicola* are described.

L. canicola infection should be considered in the differential diagnosis of unexplained pyrexia or lymphocytic meningitis.

Evidence is produced to show that the incubation period of the disease is about seven days and that the early administration of penicillin in high dosage is an effective form of therapy.

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REFERENCES

- Alston, J. M. (1949). *Proc. roy. Soc. Med.*, **42**, 707.
 Baber, M. D., and Stuart, R. D. (1946). *Lancet*, **2**, 594.
 Broom, J. C. (1951). *British Medical Journal*, **2**, 689.
 — and MacIntyre, A. B. (1948). *Vet. Rec.*, **60**, 487.
 Brunner, K. T., and Meyer, K. F. (1949). *Proc. Soc. exp. Biol. (N.Y.)*, **70**, 450.
 Campbell, A. M. G., Macrae, J., Manderson, W. G., Sumner, K. C., and Broom, J. C. (1950). *British Medical Journal*, **1**, 336.
 Fox, E. G., and Fyfe, W. M. (1951). *Glasg. med. J.*, **32**, 311.
 Heilman, F. R. (1945). *Proc. Mayo Clin.*, **20**, 169.
 Joe, A., and Sangster, G. (1951). *Edinb. med. J.*, **58**, 140.
 Kelser, K. A., and Schoening, H. W. (1948). *Manual of Veterinary Bacteriology*, p. 435. London.
 Laurent, L. J. M., Norris, T. St. M., Starks, J. M., Broom, J. C., and Alston, J. M. (1948). *Lancet*, **2**, 48.
 Mackay-Dick, J., and Watts, R. W. E. (1949). *Ibid.*, **1**, 907.
 McIntyre, W. I. M., and Montgomery, G. L. (1952). *J. Path. Bact.*, **64**, 145.
 — and Stuart, R. D. (1949). *Vet. Rec.*, **61**, 411.
 Minkenhof, J. E. (1948). *Lancet*, **2**, 8.
 Rosenbaum, H. D. (1946). *Arch. intern. Med.*, **78**, 531.
 Stagg, J. F., and Leibovitz, A. (1951). *J. Amer. med. Ass.*, **147**, 1048.
 Stuart, R. D. (1946). *Vet. Rec.*, **58**, 131.
 Virus Reference Laboratory (1953). *Lancet*, **1**, 85.
 Weetch, R. S., Colquhoun, J., and Broom, J. C. (1949). *Ibid.*, **1**, 906.

POLYAGGLUTINABILITY OF HUMAN RED BLOOD CELLS

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Amongst the abnormal agglutinations, polyagglutination is a rare phenomenon and few cases have been reported. It is a transitory agglutinability of red cells developed *in vivo* and characterized by the agglutination of cells by a proportion of normal sera independent of their group agglutinins. It is not connected with auto-agglutination.

In ABO blood grouping the so-called Landsteiner's law states that if an agglutinin is present in the red cells of a blood the corresponding agglutinin must be absent from the plasma, and if the agglutinin is absent the corresponding agglutinin must be present. The first part of this law is a logical outcome of the situation, for if both agglutinin and agglutinin were present the cells would be agglutinated (Wright, 1952), but in cases of polyagglutination this law cannot and does not stand. This factor is known to appear in some diseased states, though it has been recorded in some healthy individuals as well, but in both cases it is found to be transitory. Whether there is any influence of this polyagglutinability on the diseased process is not yet known. It is very difficult to understand what initiates this agglutinability of these cells and why the process of agglutination is inhibited *in vivo* but initiated *in vitro*.

It has been described that *in vitro* the infection in a sample of blood may change the cells in such a way that they are agglutinated by all sera (Hübener-Thomsen-Friedenreich phenomenon). Friedenreich has shown that filtrates of certain bacteria contain an enzyme which acts on human red cells, changing a latent antigen to an active one, which is known as Friedenreich's T-antigen (Race and Sanger, 1954).

Case Report

A married Hindu woman aged 30 was admitted to Chittaranjan Seva Sadan Hospital on December 28, 1953. She had had four children, but no history of miscarriage or abnormal labour. Her first baby died a few years after birth; the other three are all living and in good health. Her menstrual history was normal. The last menstrual period was September 25, 1953. She had never had any transfusion. On admission to hospital she complained of pain in the lower abdomen for 22 days, bleeding per vaginam for 22 days, and fever for two days.

On examination the patient was very anaemic. There was no jaundice. Her temperature was 102.6° F. (39.2° C.) (the high fever continued until death), pulse 140, respirations 20, blood pressure 110/80 mm. Hg. A blood count showed Hb, 36%; red cells, 2,160,000; white cells, 13,400 (polymorphs 80%, lymphocytes 12%, monocytes 8%). The urine was acid in reaction and showed no abnormality.

Pelvic abscess was diagnosed and posterior colpotomy was performed. A substance like anchovy sauce was found. Microscopical examination of this showed inflammatory cells but no malignant cells. As transfusion was advised, the serum and the washed cells (suspended in normal saline) were tested, but in spite of repeated efforts we could not determine the group. The patient was Rh-positive with