NEUROLOGICAL ASPECTS OF LEPTOSPIROSIS

BY

R. W. ROSS RUSSELL*

From the British Military Hospital, Taiping, Malaya

Since leptospirosis begins with a septicaemic stage, during which leptospirae may be isolated from the cerebrospinal fluid, the occurrence of lesions in the nervous system is not unexpected. Evidence of neurological abnormality can frequently be detected in the course of a typical attack of the disease, but it is usually insignificant compared with the involvement of other organs, and has little effect on the course or outcome of the infection.

As the world-wide distribution of leptospirosis is becoming realized, however, more clinical varieties are appearing, in some of which the nervous lesions are the dominant or the only changes. These cases have not usually been jaundiced, and the infection has been caused by leptospirae other than *L. icterohaemorrhagiae*.

A summary of the previous literature is followed by a description of the neurological complications arising in 64 personally studied cases in Malaya. All cases were proved by blood culture, positive serology, or both, and were due to a variety of leptospiral types, of which the commonest were *L. pyrogenes*, *L. hebdomidis*, *L. canicola*, *L. grippityphosa*, and *L. schüffneri*.

Observations in the Literature

The initial stages of leptospirosis are marked in over half the cases by severe headache, photophobia, and neck rigidity (Broom, 1951). Cerebrospinal pleocytosis may accompany clinical evidence of meningitis or may occur alone (Davidson and Smith, 1939; Cargill and Beeson, 1947). Rarely meningeal symptoms with optic neuritis may follow weeks or months after the initial infection (Murgatroyd, 1937).

It has been known for 40 years that leptospirosis may present as a purely meningitic illness (Costa and Troisier, 1917), and leptospiral infection accounts for a small but definite percentage of cases of benign lymphocytic meningitis (Adair, Gauld, and Smadel, 1953). Many such cases in Europe have been traced to *L. canicola*, but can also be caused by numerous other strains (van Thiel, 1948).

Meningitis cases seem to be especially common after bathing, a fact which has been thought to indicate a special portal of entry via the nasopharynx (Buzzard and Wylie, 1947), but which is probably related more to the age of the patient (Broom, 1958).

The cellular reaction in the cerebrospinal fluid may be polymorphonuclear at first, but later lymphocytes predominate (Costa and Troisier, 1917). Values for protein may show a small increase, but those for chloride and glucose are normal. The urea content is commonly raised (Robertson, 1946) in proportion to the blood level. Bile-staining may occur in icteric cases, an unusual finding in jaundice from other causes.

Lesions of the peripheral nerves and plexuses, usually of the upper limb, are not uncommon. The clinical features are pain, muscle weakness, and loss of tendon reflexes. The resemblance to anterior poliomyelitis or neuralgic amyotrophy may be close (Ramsey, 1955; Middleton, 1955).

Cranial nerve involvement has been noted on a few occasions, resulting in ocular, facial, or palatal palsies of a transient nature (Scheid, 1949). Mental confusion or even psychosis may occur (Murgatroyd, 1937; Kernohan, 1956), usually at the time of the initial illness and possibly aggravated by avitaminosis. Hemiparesis (Doherty, 1956) and subarachnoid haemorrhage (Buzzard and Wylie, 1947) are rarities.

The literature contains only nine cases of spinal cord involvement (Creyx, Georget, and Bonnel, 1935; Labbé, Boulin, Uhry, and Ullman, 1935; Joosten, 1936; Hegler, 1936; Fontan, Dupin, and Verger, 1938; Mortenson, 1940). Symptoms are mainly motor, involving the legs and often accompanied by retention of urine. The outcome may be fatal (Labbé *et al.*); recovery may be uneventful (Creyx *et al.*) or slow and incomplete (Hegler). The strain of leptospira involved is variable.

Meningitis

Meningitis Complicating Leptospirosis.—Of 64 patients examined, all complained of headache

*Present address: Department of Neurology, Radcliffe Infirmary, Oxford.

during the initial febrile illness. In addition 19 patients (30%) complained of photophobia and 34 (54%) had some degree of nuchal rigidity. Eleven patients (18%) had nuchal rigidity of a degree sufficient to warrant a clinical diagnosis of meningitis, and in these patients lumbar puncture was carried out partly to exclude the presence of a purulent meningitis, partly to establish the nature and frequency of cerebrospinal fluid changes, and partly as a therapeutic measure to relieve the headache.

The findings in the 11 cases are summarized in Table I.

TABLE I
C.S.F. FINDINGS IN 11 CASES OF LEPTOSPIROSIS
COMPLICATED BY MENINGEAL FEATURES

Case No.	Day of Disease	Fluid	Cells per c. mm.	% Poly-morphs	% Lympho-cytes	Protein (mg./100 ml.)
14	8	Turbid	120	80	20	35
55	7	Turbid	200	0	100	80
50	7	Turbid	60	20	80	120
51	2	Clear	4	—	—	35
48	6	Clear	1	—	—	50
42	4	Clear	1	—	—	20
40	7	Clear	2	—	—	30
39	4	Clear	1	—	—	50
29	20	Clear	2	—	—	30
	Relapse 30	Clear	4	—	—	45
45	Relapse 4	Clear	4	—	—	30
1	3	Clear	4	—	—	45

With one exception (Case 29) lumbar puncture was performed during the initial stage of the illness at the time when meningitic signs and symptoms were at a maximum. Cerebrospinal fluid pleocytosis was found in three out of 11 cases, and slight elevation of the protein (>40 mg. per 100 ml.) level in a further four. Chloride and glucose values (not included in Table I) were normal. Case 29 developed marked meningitic signs and symptoms during a relapse in the third and fourth weeks of illness, but no abnormality was found in the cerebrospinal fluid. Headache, anaemia, and general lassitude persisted for eight weeks.

With the exception of Case 29 meningitic symptoms were transient, lasting two to six days and going on to complete recovery.

These findings are in agreement with those of previous workers. The predominance of polymorphs in the differential cell count in Case 14 is noteworthy. The slight elevation of protein in Cases 1, 29, 39, and 48 may be within the limits of laboratory error, and so of no significance.

Meningitis as Dominant Feature (Meningitis Leptospirosa).—Three cases presented with an illness which was predominantly meningitic, the nature of which was recognized only in the light of routine serological testing.

Case 58.—This patient, a man, aged 19, was admitted on January 12, 1956, the second day of illness, complaining of severe headache, backache, and photophobia. Ten days previously he had been duck shooting in swampy ground, his legs being immersed in water for some hours at a time, but the rest of his body had remained dry. On examination his temperature was 102°F . and his pulse 110 per minute. He had marked rigidity of the neck and back, the fauces were congested, the calf and thigh muscles were tender, and the spleen tip was palpable. There was no conjunctival or ciliary injection and no abrasions or jungle sores on the legs. The knee and ankle jerks were absent and there was weakness of all muscle groups in the lower limbs, maximal in the quadriceps and plantar flexors of the foot.

A blood count showed: white blood cells 6,800 per c.mm. (polymorphonuclears 60%, lymphocytes 36%, monocytes 4%). A trace of protein was found in the urine. The serum bilirubin level was 0.6 mg. per 100 ml. blood urea 40 mg. per 100 ml. The C.S.F. (fourth day of disease) contained 110 cells per c.mm. (all lymphocytes) 90 mg. protein per 100 ml., 50 mg. glucose per 100 ml. 720 mg. chlorides per 100 ml. A blood culture was positive.

Anterior poliomyelitis was diagnosed, and treatment was on symptomatic lines only.

The patient was febrile for 48 hours after admission and had a slight secondary fever of 99.2°F . on the fourth day. Weakness and tenderness of all muscle groups in both lower limbs was present for one week. The knee and ankle jerks returned after five days, but remained sluggish for two weeks, by which time symptomatic recovery was complete. There were no sequelae.

Case 56.—This Gurkha soldier, aged 26, was seen on September 28, 1955, the sixth day of illness, complaining of headache, severe pain in the legs, neck stiffness, vomiting, and slight abdominal pain. For the previous three weeks he had been engaged in jungle ambush work in the Ipoh area under damp conditions. His temperature was 104°F . and pulse 110 per minute. There were no abnormal physical signs apart from nuchal rigidity and muscular tenderness. Small jungle sores were noted on the shins.

A blood count showed: white blood cells, 11,200 per c.mm. (polymorphonuclears 92%, lymphocytes 8%). The urine contained protein +, occasional white cells, and casts. The C.S.F. (eighth day of disease) showed 6 cells per c.mm., all lymphocytes, and 60 mg. protein per 100 ml.

Complement fixation and agglutination reactions were positive.

The clinical diagnosis on admission was anterior poliomyelitis, and treatment was on symptomatic lines only.

Fever subsided after 10 days of illness and the patient was asymptomatic after two weeks. There were no sequelae.

Case 57.—This Gurkha rifleman, aged 23, in the same company as Case 56, was referred to hospital on October 3, 1955, with the complaint of headache, vomiting, and

TABLE II
SUMMARY OF C.S.F. FINDINGS IN THREE CASES OF MENINGITIS LEPTOSPIROSA

Case No.	Day of Disease	Fluid	Cells	% Polymorphs	% Lymphocytes	Protein (mg. per 100 ml.)	Chloride (mg. per 100 ml.)	Glucose (mg. per 100 ml.)
58	4	Turbid	110	—	100	90	720	50
56	8	Clear	8	—	100	60	—	45
57	7	Turbid	280	80	20	85	720	45
	14	Clear	1	—	—	30	—	—

cough for six days. On examination his temperature was 101°F. and pulse 70 per minute. He appeared drowsy and confused with marked nuchal rigidity and muscular tenderness in the legs. The knee and ankle jerks were sluggish.

A blood count showed: white blood cells 10,300 per c.mm. (polymorphonuclears 84%, lymphocytes 10%, monocytes 6%). The urine appeared normal. The C.S.F. (seventh day of disease) contained 280 cells per c.mm. (polymorphonuclears 80%, lymphocytes 20%), 85 mg. protein per 100 ml., 45 mg. glucose per 100 ml., and 720 mg. chlorides per 100 ml. On the fourteenth day of disease cells had fallen to 1 per c.mm., and protein to 30 mg. per 100 ml. Complement fixation and agglutination reactions were positive.

The clinical diagnosis on admission was anterior poliomyelitis, and treatment was on symptomatic lines only.

The fever continued for 36 hours after admission, and there were no symptoms or signs after three days. Tendon reflexes returned to normal and there were no sequelae.

These cases illustrate the value of routine serological testing in patients with lymphocytic meningitis. There was little to suggest a diagnosis of leptospirosis on admission, although it is significant that two of the three cases had proteinuria.

Peripheral Nerve Lesions

Two patients presented unequivocal evidence of peripheral neuritis during the course of leptospirosis.

Case 48.—This man, aged 24, suffered a mild attack of leptospirosis, being febrile for nine days. He was admitted on the fourth day of illness, at which time neck stiffness was a prominent sign and lumbar puncture was performed, the fluid being normal. During the acute phase of the illness and for five days after the fever had subsided he complained of severe neuralgic pain in the distribution of the fifth and sixth cervical nerves on the right side. He also complained of pain and numbness in both lower limbs for the first three days. Tendon reflexes were diminished in the right arm and there was some weakness of the triceps muscle on that side, but no sensory loss and no objective findings in the legs. Complement fixation and agglutination reactions were positive.

Treatment was symptomatic and recovery was complete in two weeks.

Case 29.—This patient, aged 28, was admitted on May 10, 1955, with a moderately severe attack of leptospirosis, being febrile for 14 days and having a

relapse with meningism during the fourth week. On the fifteenth day of illness he developed paraesthesiae in both feet which lasted for five days. This was succeeded by a severe aching pain over the distribution of the fourth and fifth cervical nerves on the left side. There was weakness of the deltoid and biceps muscles on that side and the biceps and supinator reflexes were diminished. No sensory loss was demonstrable.

Complement fixation and agglutination reactions were positive.

Treatment was symptomatic and recovery was complete in six weeks.

The clinical syndrome in the above cases is similar to neuralgic amyotrophy which may follow serum injections. The lesion may be in the brachial plexus.

A Case of Spinal Involvement

One case was complicated by an ascending myelitis of an extent not previously reported. Full details are therefore given.

Case 64.—The patient, aged 19, was in good health until May 11, 1956, when during a jungle patrol he developed a severe frontal headache, diarrhoea, and fever. After three days he came out of the jungle and was seen by the regimental medical officer, who immediately arranged his admission to hospital. On arrival his general condition was poor. He was unable to sit up and complained of headache and abdominal pain. His temperature was 101°F. and his pulse 90 per minute. There was marked conjunctival and scleral injection, acutely tender calf muscles, scattered rhonchi over both lung fields, and ill-defined tenderness in the right upper quadrant of the abdomen. Slightly enlarged, painless lymph nodes were palpable in all areas. The provisional diagnosis was leptospirosis. The haemoglobin was 11.9 g.%, white blood cells 15,200 per c.mm. (polymorphs 80%, lymphocytes 20%). Blood urea was 75 mg. per 100 ml. On the evening of the day of admission he was noticed to have a mild degree of neck stiffness and slight weakness of the legs, affecting all the muscle groups. The tendon reflexes were present and equal. He had some difficulty with micturition and the bladder was palpably enlarged.

On the following day the neck stiffness was more pronounced and the muscular weakness had spread to involve the trunk and arms, the legs still being more severely affected. Reflexes were just obtainable and there was no sensory loss. Coordination in the arms was normal but could not be tested in the legs owing to the weakness. He was mentally clear but extremely anxious. Coarse nystagmus was present on lateral gaze, but apart

from this the cranial nerves appeared normal. Respirations were rapid and shallow and towards evening were clearly becoming inadequate; no movement was appreciable in the lower part of the chest and the accessory muscles of respiration were active. There was slight central cyanosis. Swallowing and speaking were unaffected at this stage, and blood pressure was well maintained. He had by this time developed acute retention of urine and required intermittent catheterization. Twenty-four hours after admission he was placed in a Drinker respirator, and after a short period of alarm he was able to adapt himself to its movements.

At this time he was thought to have anterior poliomyelitis or acute infective polyneuritis, and after 36 hours it was clear that the upward spread of paralysis was still progressing. For a period of six hours his speech was affected, becoming weak and nasal in quality, and swallowing was achieved only with slight choking and spluttering. There was almost complete paralysis of respiration, which unaided took the form of irregular diaphragmatic gasping contractions every five to 10 seconds. There was no intercostal element, and the respirations were accompanied by a marked tracheal tug.

The respirator was tilted head-down at an angle of 15° and the posterior pharynx aspirated at intervals, but paralysis of swallowing was never complete enough to make pooling of secretions a major problem.

Apart from this evidence of bulbar damage he developed a defect of conjugate lateral movement of the eyes. Although he appeared confused and slightly euphoric there was no marked disturbance of consciousness, and he complained of cramps in the limbs and abdominal pains, which were ascribed to spasm of the abdominal muscles. He lay with legs extended and feet plantar-flexed, arms flexed at elbow and wrist, and with adduction and internal rotation at the shoulder. A constant coarse fasciculation was present in the muscles of the shoulder girdle, and there was sometimes a coarse clonic twitching in the pectoralis major on both sides, violent enough to move the whole upper limb. Muscle tone was diminished in all but the pectoral group, power was grossly reduced, tendon reflexes in all limbs were lost, and plantar responses were extensor. Bladder control was still defective, and an indwelling catheter was introduced, urine being released every four hours. All modalities of sensation were diminished over the lower part of the body, an ill-defined sensory level being present at the costal margin.

In summary, there was evidence of an acute infection of the spinal cord spreading in the course of 48 hours to involve the medulla and mid-brain, and affecting the motor neurones, long sensory tracts, and pyramidal fibres.

Treatment at this stage was supportive, and aimed at the prevention of skin, pulmonary, and urinary complications, but in spite of prophylactic sulphonamides and a large fluid intake he developed a *Bact. coli* infection of the urinary tract which was difficult to eradicate. A careful watch was kept on the cardiovascular system, but apart from a constant tachycardia of 100 to 110 there were no other signs and the blood pressure remained steady at a normal figure.

After progressing rapidly for 48 hours the paralysis began to recede slowly. The patient was taken out of the respirator for increasing periods each hour, and by the fourth day was fit enough to breath without it. Power slowly returned to his limbs and the tendon reflexes reappeared. The trunk muscles regained their tone, and by the tenth day he was able to sit up. Perception to pin-prick remained diminished in the legs for 10 days.

At the end of a month there was only a slight generalized diminution of muscle power, but the urinary infection persisted and resulted in the formation of a urethral stricture which eventually required surgical treatment. He also had a mild residual normochromic anaemia (haemoglobin 10.1 g. %). Examination of the cerebrospinal fluid after six weeks showed no abnormality apart from a raised protein level (90 mg. per 100 ml.).

Fletcher's culture for leptospirosis was performed on the blood at the time of admission and was read at 15 and 25 days, leptospirae being seen on both occasions. Unfortunately the culture became secondarily infected, and further identification of the serological type of the organism was not then possible.

TABLE III
C.S.F. FINDINGS IN CASE 64

Day of Disease	4	16	42
Appearance	clear	clear	clear
Cells (per c.mm.)	25	1	1
Polymorphs (%)	60	—	—
Lymphocytes (%)	40	—	—
Protein (mg. per 100 ml.)	110	124	90
Chlorides (mg. per 100 ml.)	720	740	740
Glucose (mg. per 100 ml.)	43	46	70

Culture of the cerebrospinal fluid on blood-agar was sterile on all occasions.

Serological specimens were taken on the ninth, 16th, and 25th days, and were tested at the Wellcome Laboratories, using the agglutination technique. The ninth and sixteenth day specimens were positive to 1 in 100 with the following strains: *L. autumnalis*, *L. bangkinang*, *L. javanica*, *L. hebdomidis*, *L. pomona*. The 25th day specimen reacted with the same strains to 1 in 1,000 but were not tested to higher dilutions.

A similar rapid upward spread of the paralysis with transient brain-stem involvement sometimes occurs in acute infective polyradiculitis. Muscle fasciculation is sometimes observed in this condition, and in paralytic poliomyelitis at the time of destruction of the anterior horn cells, but seldom to such a degree as in this patient.

Had the nasopharyngeal paralysis lasted for more than a few hours secretions would probably have been inhaled. Probably better treatment would have been an elective tracheotomy at an earlier stage and insertion of a cuffed endotracheal tube.

Discussion

One of the striking features in the literature and the cases reported here is the extent of neurological damage which is compatible with complete recovery.

Even the most complete and extensive paralysis, as in Case 64, appears to carry a good prognosis if the patient can be kept alive during the initial stages.

The nature of the neurological lesions must remain in doubt. In a disease characterized by a haemorrhagic tendency it might be expected that complications of a vascular nature would occur. With the possible exception of peripheral neuritis, which has been ascribed to haemorrhage into the nerve sheaths (Kramer, 1926), none of the cases described in the present series has any features to suggest single haemorrhage from a large vessel or multiple haemorrhage from small vessels, and apart from the case with subarachnoid haemorrhage described by Buzzard and Wylie (1947) and the hemiplegic patient mentioned by Doherty (1956), vascular lesions are conspicuously lacking in the literature.

Clinical and pathological evidence of acute meningitis in the initial stages is a common finding and is attributable to the presence of leptospirae in the cerebrospinal fluid. However, in the few cases of leptospirosis with neurological involvement which have come to necropsy, there has been no suggestion of a progressive exudate or fibrotic process such as occurs in pyogenic or tuberculous meningitis. van Thiel (1948) has suggested that leptospirae are unable to proliferate in the meninges.

Changes in the parenchyma of brain, brain-stem, and spinal cord are equally inconspicuous. Leptospirae have been demonstrated in the cerebral cortex (Bingel, 1936), and occasionally microscopic evidence of inflammation with nerve cell degeneration similar to that seen in encephalitis lethargica (Koppisch and Bond, 1952), but the usual finding is minimal perivascular infiltration with lymphocytes in the hippocampus, medulla, cerebellum, and basal ganglia. Neither anterior horn cell damage nor demyelination is evident.

There is, however, some clinical resemblance between certain of the neurological sequelae of leptospirosis, notably myelitis, and the nervous complications of smallpox, measles, varicella, vaccination, or other prophylactic inoculations, all of which have been ascribed to a non-specific allergic reaction of the nervous system to various antigens, chiefly bacterial or viral (Miller and Evans, 1953), and have been reproduced experimentally (Lumsden, 1949).

Points of similarity between these post-infective encephalo-myelitides and the sequelae of leptospirosis are the latent interval after infection, the rapid onset of widespread spinal damage, the relatively small meningeal reaction, and the possibility of complete recovery. However, the absence of drowsiness, convulsions, other signs of encephalitis, and the lack of histological evidence of demyeli-

nation in fatal cases does not support such a theory (Koppisch and Bond, 1952).

The case of ascending mesencephalomyelitis described in the present series is of a type not previously reported. The paralysis spread rapidly to involve the respiratory muscles and motor cranial nerves in medulla and brain-stem as high as the mid-brain. The disease bore some resemblance to acute infective polyradiculitis in its rapid symmetrical onset and upward spread, its predominance of motor over sensory involvement, and the high protein levels in the cerebrospinal fluid. Against this were the absence of facial involvement, the occurrence of external ophthalmoplegia, the marked sphincter disturbance, the presence of extensor plantar responses, and the relatively rapid recovery, all unusual features of polyradiculitis.

The fact that full recovery can occur in this condition makes management of the paralysed patient all the more important, since faulty treatment may be worse than no treatment at all. This is particularly the case if bulbar weakness supervenes on diaphragmatic and intercostal paralysis, when assisted respiration of the type provided by the standard tank respirator may aspirate pharyngeal secretions into the lungs. In the present case, although a slight degree of palatal weakness developed, there was no serious interference with the swallowing mechanism. Tipping the patient with frequent aspiration of the pharynx were sufficient to prevent accumulation of secretions during the short period of bulbar paralysis.

Should the paralysis persist, however, experience with poliomyelitis in Denmark and elsewhere has shown that the ideal treatment for the combined respiratory and pharyngeal form is early tracheotomy with intermittent positive pressure respiration (Smith, Spalding, and Russell, 1954). There is no danger of inhalation and the arrangement permits of easy aspiration of the trachea and bronchi. Such treatment could be life-saving on the rare occasions when leptospirosis is complicated by spinal cord and brain-stem involvement.

Summary

The various types of neurological disorders occurring in leptospirosis are reviewed from previous reports. There are four main groups in order of frequency:

- (a) Meningitis which may be early or late and may occur either as a secondary complication of an attack of leptospirosis or as the primary feature of the illness.
- (b) Peripheral nerve lesions, usually a late complication, affecting the proximal muscles of the upper limbs.

- (c) Cortical and cranial lesions, rare and unimportant features usually occurring in severe infections.
- (d) Spinal cord lesions, which are also rare and consist of transverse or ascending forms of myelitis.

The neurological lesions in the present series are described. There were 11 cases with symptoms and signs suggestive of meningitis, which occurred during a typical attack of leptospirosis. Three had cerebrospinal pleocytosis and in a further four the cerebrospinal fluid protein level was raised.

Three cases of meningitis leptospiroica are described in which the illness was predominantly meningitic throughout.

Two cases of peripheral neuritis are described, both affecting the upper limbs.

One case of rapidly ascending mesencephalomyelitis affecting the motor and sensory functions of the spinal cord and brain-stem as high as the mid-brain is described.

All patients recovered completely from the neurological sequelae.

The manner in which leptospirosis damages the nervous system is discussed.

The acute inflammatory reaction is a result of the invasion of the meninges by leptospirae. The inflammation is lymphocytic and is not followed by fibrosis.

There is little to favour a vascular aetiology in the later neurological complications. However, there are some features of myelitis which suggest that it

may be an allergic response on the part of the nervous system.

The management of patients with bulbar lesions is briefly discussed, and early treatment with a mechanized positive pressure respirator combined with tracheotomy is recommended.

I wish to thank the Director of Medical Services, R.A.M.C., for permission to publish this report.

REFERENCES

- Adair, C. V., Gauld, R. L., and Smadel, J. E. (1953). *Ann. intern. Med.*, 39, 675.
- Bingel, A. (1936). *Dtsch. Z. Nervenheilk.*, 141, 133 (quoted by Mortenson, 1940).
- Broom, J. C. (1951). *Brit. med. J.*, 2, 689.
- (1958). Personal communication.
- Buzzard, E. M., and Wylie, J. A. H. (1947). *Lancet*, 2, 417.
- Cargill, W. H., and Beeson, P. B. (1947). *Ann. intern. Med.*, 27, 396.
- Costa, S., and Troisier, J. (1917). *Presse méd.*, 25, 189.
- Creux, A., Georget, P., and Bonnel, H. (1935). *J. Méd. Bordeaux*, 112, 527.
- Davidson, L. S. P., and Smith, J. (1939). *Brit. med. J.*, 2, 414.
- Doherty, R. L. (1956). *Aust. Ann. Med.*, 5, 23.
- Fontan, A., Dupin, J., and Verger, P. (1938). *J. Méd. Bordeaux*, 115(1), 497.
- Hegler, C. (1936). *Dtsch. Z. Chir.*, 248, 190.
- Joosten, A. J. (1936). *Ned. T. Geneesk.*, 80, 1821.
- Kernohan, R. J. (1956). *Brit. med. J.*, 1, 1342.
- Koppisch, E., and Bond, W. M. (1952). Section of Pathology, Symposium on the Leptospiroses. Army Med. Service Graduate School. Walter Reed A. M. C., Wash., D.C.
- Kramer, P. H. (1926). *Ned. T. Geneesk.*, 70(2), 1942 (quoted by Walch-Sordrager, 1939).
- Labbé, M., Boulon, R., Uhry, P., and Ullman, B. (1935). *Bull. Soc. méd. Hôp., Paris*, 59, 1504.
- Lumsden, C. E. (1949). *Brain*, 72, 198.
- Middleton, J. E. (1955). *Brit. med. J.*, 2, 25.
- Miller, H. G., and Evans, M. J. (1953). *Quart. J. Med.*, 22, 347.
- Mortenson, V. (1940). *Lancet*, 1, 117.
- Murgatroyd, F. (1937). *Brit. med. J.*, 1, 7.
- Ramsey, A. M. (1955). *Ibid.*, 2, 24.
- Robertson, K. (1946). *Ibid.*, 2, 810.
- Scheid, W. (1949). *Fortschr. Neurol. Psychiat.*, 17, 295.
- Smith, A. C., Spalding, J. M. K., and Russell, W. R. (1954). *Lancet*, 1, 939.
- Thiel, P. H., van (1948). *The Leptospiroses*. Universitaire Pers. Leiden.