NEPHRITIS IN THE DOG
ASSOCIATED WITH
LEPTOSPIRA CANICOLA INFECTION

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by

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Index

Section 1.

A description of the naturally occurring disease in the dog associated with infection by Leptospira canicola, including bacteriological and serological findings.

Introduction

1. Historical

In 1899 Klett of Stuttgart (cited by Jenny and Kanter, 1946) described a clinical syndrome in the dog which was characterised by apathy, stomatitis and gastroenteritis. The term Stuttgart disease seems to have been used ever since in Britain to describe the uraemia and toxic effects of Leptospira canicola infection.

It was not until over 20 years had elapsed that Lukes and Debrek (1923) (cited by Hyhlik, 1924) showed that the syndrome known as Stuttgart disease was associated with a spirochaetal infection. During an epidemic of Stuttgart disease in Vienna in 1922-23 they demonstrated spirochaetes in the organs of nine dogs which died. In 1924 two other workers Hyhlik and Krivacek, both working in Lukes' department, added further to the total of dogs dying of Stuttgart disease in which spirochaetes were demonstrated.

spirochaetes in three out of 13 dogs which were not thought to have Stuttgart disease but metritis, distemper and chronic eczema respectively. He criticised Lukes for stating that the spirochaetes were a specific cause of Stuttgart disease and suggested that they might be the intestinal parasites of distemper being excreted by the kidneys.

In a much fuller work in 1925 Lukes produced more evidence. Sappier, Nahano, Yamamoto and Horalek working in Lukes' Institute found spirochaetes in 97 of 105 cases, the organisms being found singly or in clumps in tubules near the glomeruli often in enormous masses. They were usually confined to the cortex. He emphasised the need for adequate formol fixation before examining tissues for spirochaetes. He refuted Klarenbeek's suggestion that these spirochaetes were intestinal in origin and stated that those were always shorter and thicker than the organisms found in Stuttgart disease.

Lukes had also examined 30 control dogs and found no spirochaetes and used this evidence to refute Wirth's suggestion that the leptospires were non-specific. He found great difficulty in culturing the organisms chiefly, he stated, because of the growth of contaminants but he did succeed in growing one strain through three subcultures. In the latter

part of the article Lukes compares this disease to Weil's disease, another spirochaetosis. The main clinical differences mentioned by Lukes were the presence of icterus in Weil's disease but only in occasional cases of Stuttgart disease and the presence of fever, diarrhoea and necrotic patches in the mouth in Stuttgart disease but not in Weil's.

He thought dogs obtained the infection as a venereal disease but considered that the swallowing of infected excretions might also play a part. He found it difficult to transmit to dogs, rabbits and guinea pigs. He could infect the guinea pig in only 50% of cases producing polyuria, thirst and leptospires in the kidneys. He also attempted to give Stuttgart disease a new name - Spirochaetosis melaenogenes canum. 8

In another publication, Lukes, along with Jelinek and Schramek described in some detail six chronic cases all of which had spirochaetes in the kidneys but three of them appear to have been more of a sub-acute type. Three definitely chronic cases were dogs of two, four and five years of age and spirochaetes were found in the kidneys only after prolonged search. These six animals were all known to have survived an acute attack of Stuttgart disease. They discussed the possibility that a primary attack of Stuttgart disease could give rise to chronic nephritis.

acute jaundice, uraemia, chronic uraemia, polyuria and symptomless leptospiruria curing itself or progressing to a fatal uraemia. Wirth did not serologically differentiate the leptospiral infections and the first two groups were probably due to L. icterohaemorrhagiae infections and the remaining renal syndromes to L. canicola.

Other European surveys of the incidence of infection with L. canicola were published about this time. Uhlenhuth and Zimmermann (1936) found 15-20% of dogs infected with Leptospirae, two-thirds with L. canicola. Walch-Sorgdrager (1939) showed that 40% of 414 Dutch dogs suspected of having leptospirosis had positive titres to L. canicola and 26% to L. icterohaemorrhagiae. Babudieri and Castagnoli (1940) found only two out of 159 canine sera positive for L. canicola and 54 for L. icterohaemorrhagiae.

In Britain interest in canine spirochaetosis was first aroused in 1925 by Okell, Dalling and Pugh when they experimentally reproduced Weil's disease in the dog. They demonstrated two clinical forms of leptospirosis; one a hyperacute haemorrhagic type and another showing an icteric picture with either an acute or insidious onset. They also pointed out that this second group might show only mild fever and fleeting gastro-intestinal symptoms. The spirochaete with which they

worked behaved in the guinea pig in a similar fashion to the one found in the rat and we must presume that the strain was L. icterohaemorrhagiae although these workers did not carry out serological tests to identify the strain.

This work was rightly received with great acclaim at the time but unfortunately it served to obscure in Britain the attempts being made in Europe by Lukes and others to draw attention to the possibility of there being a different strain of spirochaete causing a primarily uraemic syndrome. It was over 20 years before Stuart (1946) drew attention to the fact that in 40% of bloods from 101 dogs in Glasgow he had found agglutinins against L. canicola. The results of clinical examinations were not available to him but in this paper he hypothesised much that has since proved to be true of the disease as it occurs in dogs in this country.

The Stuart survey was largely responsible for stimulating the work embodied in this thesis. From October 1947 to December 1948 149 dogs were found to have serological evidence of infection with Leptospira canicola. Leptospires were found in the urine of 37 of these cases and in six bloods. Strains were isolated in culture from both blood and urine. These results were first reported by McIntyre and Stuart (1949).

Meantime another serological survey had been carried out

by MacIntyre and Broom (1948) showing that the sera of 42% of 416 dogs examined had shown agglutinins against Leptospira canicola.

In November 1947 a short work was published by Joshua and Freak describing the specificity of penicillin therapy in six cases of uncomplicated primary Leptospirosis canicola. In the absence of spirochaetes being demonstrated in any of those cases none of the agglutination titres published provides sufficient evidence of primary infection.

In 1948 Mills published a report of her findings in 30 dogs 19 of which showed blood agglutinins against leptospirae. Much of the interpretation of results in this paper can not be borne out by the evidence presented as too much reliance was placed on physical examination and history of cases without fully considering the serological findings and biochemical assessment of renal function.

Lauder 1950 confirmed the classification of the disease given by McIntyre and Stuart (1949) but very rightly pointed out the difficulty of distinguishing on a purely physical examination mild primary cases from secondary cases without uraemia. He emphasised the importance of using serological examinations in conjunction with blood urea estimations.

Joshua (1949 and 1950) has supplied the only other clinical

description of the disease as it occurs in this country. This worker divided primary cases into five clinical groups - acute, subacute, mild, atypical and subclinical, the latter being a hypothetical group representing animals shedding leptospires in the urine without any clinical manifestation. The mild group showed only mild malaise and polyuria while the atypical was not very adequately described. The acute cases were characterised by a short, severe illness lasting only 12-48 hours. The animals were afebrile and suffered from a great thirst which appeared to produce severe emesis followed by another bout of drinking. The subacute were characterised by grossly enlarged kidneys, thirst and a varying degree of apathy. The absence or presence in low dilutions of agglutinating antibodies in the sera of many of the cases described by this author suggests that they were not in the primary stage of L. canicola infection. Joshua also doubted the existence in the London area of the bacteraemia described by McIntyre and Stuart (1949) as it occurred in dogs in Edinburgh and stated that the detection of leptospiruria as described by these workers was impracticable for the practising veterinary surgeon. Some cases of suspected chronic nephritis associated with low titres are also described. No histopathological details accompany this work.

In America the first work of importance was carried out by Bloom (1941) in which he described the clinical disease in nine dogs. He found albuminuria and tubular casts, marked nitrogen retention (106-206 mg./100 ml.) and a polymorphonuclear leucocytosis. Five cases were icteric. Unfortunately his agglutination techniques were not very successful and it is impossible to assess whether he was describing infections of icterohaemorrhagiae or L. canicola.

In 1944 Coffin and Stubbs reviewed the European work and gave a description of Leptospirosis canicola as it occurred in the U.S.A. They described a primary and secondary stage, the former being characterised by pyrexia, stiffness of the hindquarters and ulceration of the mouth. Also found were albumin, a variety of tubular casts, and bilirubin in a urine of high specific gravity. A leucocytosis varying from 18,000-50,000 per c.mm. was also regarded as characteristic. Coffin and Stubbs asserted that emaciation then followed and that dogs continued into the secondary stage and died in uraemia.

Beaman (1952) published a summary of the clinical findings in 64 cases and in which he stated that he recognised the transition from the primary to the secondary stage. The clinical signs which he thought most significant were emesis, thirst, polyuria or oliguria in severe cases, albuminuria,

uraemia (as high as 475 mg./100 ml.), leucocytosis and an increased erythrocyte sedimentation rate.

When the work embodied in this thesis was commenced in 1947 there were descriptions by various European workers of the histopathology of so-called Stuttgart disease as it occurred in central Europe. Klarenbeek and Schuffner, in Holland, had isolated and typed a strain of leptospira from cases showing the same clinical syndrome which was different serologically from L. icterohaemorrhagiae and which they named L. canicola. They, and Wirth in Vienna, had succeeded in experimentally infecting dogs. In Britain there was serological evidence, based on surveys of two dog populations, to show that about 40% of these had agglutinins against L. canicola. There was no detailed clinical description of the disease as it occurred in this country and no attempt had been made to associate cases of nephritis with infection by L. canicola. Furthermore, L. canicola had not been isolated from dogs in Britain and no study of the incidence of leptospiruria had been made. It was, therefore, with a view to identifying the causal organism and to correlating the clinical manifestations with the serological, biochemical and histopathological findings that the work in this thesis was undertaken.

2. Classification

As it proved impossible to classify many cases accurately on physical signs only, agglutination titres and blood urea levels have been used to assess both the severity and the duration of the illness.

All cases having an agglutination titre against L. canicola of 1/10,000 or higher were classified as being in the primary renal stage. Any case showing a rise of titre on two successive examinations, e.g. 1/1,000 to 1/3,000 were regarded as being primary. In addition a few cases which were examined only once and had titres of 1/3,000 were classified as primary because of evidence of leptospiruria or histopathological evidence gained from autopsy. All dogs having persistently lower titres, 1/30, 1/100, 1/300 or 1/1,000 were classified as being in the secondary stage.

Primary cases have been subdivided into mild, severe and most severe groups according to the levels of blood urea. The particular degrees of nitrogen retention were chosen because they most consistently agreed with the degree of severity suggested by the physical signs and rate of recovery of the animals concerned. Cases having a blood urea of up to 50 mg./100 ml. were classified as being mild; from 50-200 mg./100 ml. as being severe; and over 200 mg./100 ml. as being

most severe.

Histological examination of autopsy material available confirmed the accuracy of this classification. In a few cases classified as primary because of agglutination titre it was found that fibrosis had begun to replace some of the acute interstitial infiltration and therefore they would be better described as subacute.

Cases in the second stage have also been divided into two groups - those with nitrogen retention and those without. Animals with a blood urea level of over 50 mg./100 ml. were regarded as having nitrogen retention.

Materials and Methods

The 369 cases which form the basis of the description of the clinical disease were all dogs which were taken to the small animal clinic of the Royal (Dick) School of Veterinary Studies during the years 1947-51. On first examination those cases were tentatively diagnosed as being affected with leptospiral nephritis on the evidence of the owner's history and a physical examination. Samples of urine and blood were then taken to the laboratory for confirmation. The majority of the animals were treated with penicillin or streptomycin together with supportive treatment in cases of emesis and dehydration. This treatment involved the return of the animal to the clinic thus giving further opportunities for study of the course of the disease. Repeated urine and blood examinations were made in many cases.

In the early part of the investigation the laboratory examinations were carried out with the primary aim of establishing the aetiological factor and the degree of severity of the disease. Estimation of the urea content of the blood was performed using the Urease and Nesslerisation method as described by Harrison (1947) using the serum of the affected case. Agglutination tests were carried out by Schuffner's method as described by Davidson et al. (1934). Living leptospiral

cultures were mixed with small volumes of the test serum in a series of ascending dilutions and after a period of incubation, usually overnight, drops of the respective mixtures were examined by dark ground methods for the presence of agglutination or lysis. Leptospirae are agglutinated by the lower dilutions of a specific antiserum and lysed by the higher so that in each case the titre of the serum is represented by the highest dilution in which demonstrable lysis occurs. All sera were tested against a strain of both Leptospira canicola and Leptospira icterohaemorrhagiae. The range of dilutions used was 1/10, 1/30, 1/100, 1/300, 1/1,000, 1/3,000, 1/10,000, 1/30,000. During the first part of the investigation the agglutination tests were carried out by R. D. Stuart M.D., D.Sc., of the Royal Infirmary, Glasgow. Later when Dr. Stuart's assistance was no longer available the author carried out this examination. Samples of blood from 58 dogs which had a pyrexia of 104^{o} F or over of unknown etiology were sent to Dr. Stuart's laboratory for culture. Those blood samples were taken with liquoid venules (Bayer Products, Ltd. 3D) from the cephalic vein after the skin had been cleaned and treated with an antiseptic.

All urine samples were obtained by catheterisation and examined by dark ground microscopy for the presence of

spirochaetes. For this purpose gum elastic catheters, varying in diameter according to the size of the dog, were used. These were boiled before use for five minutes along with the stilette. All dogs were catheterised in a standing position and this procedure was found to be relatively simple and harmless to the animal concerned. A vaginal speculum and headlamp were used to facilitate catheterisation in the female. The urine was drawn into a clean universal container and taken to the laboratory for examination. A drop of urine was placed on a coverslip and after all air bubbles were pricked it was covered with a slide. The greater part of the area of the coverslip was then examined for spirochaetes. In 10 cases of leptospiral infections known to have been present for several years the urine was submitted to centrifugation at 6,000 revolutions per minute and the resultant deposit examined for spirochaetes by dark ground microscopy. Six urines were submitted to cultural examination. Proteinuria was detected by the salicyl-sulphonic acid layer test in which 20% salicyl-sulphonic acid was placed in a small test tube to a depth of at least half an inch and a layer of urine carefully pipetted on to its surface. In the presence of protein a grey ring is formed at the junction of the two liquids. This proved to be more sensitive than either the turbidity test using salicyl-sulphonic acid or the

heat test with nitric acid. As little as 5 mg./100 ml. protein could be detected by this method. In the later stages of the investigation a quantitative estimation of the protein was made using King's (1946) turbidity standards. A deposit was obtained by centrifugation of 10 ml. of urine at 3,000 revolutions per minute for five minutes and examined for the presence of cells and renal tubular casts. In Table 1 are given the numbers of cases submitted to the above examinations at least once along with a statement of the total number of these examinations carried out.

Table 1

	Agglutination Test	Blood Urea	Lepto-spiruria	Proteinuria and deposit
No. of cases examined at least once.	369	369	320	250
Total no. of examinations carried out.	682	851	694	465

Haematological examinations carried out included measurement of the percentage of haemoglobin using the Sahli haemoglobinometer and the enumeration of erythrocytes and leucocytes per c. mm. A differential leucocyte count was made by examining 100 cells in a blood film treated with Leishman's stain. In some cases the erythrocyte sedimentation rate (B.S.R.) and

packed cell volume (P.C.V.) were measured.

A summary of the clinical examination has been recorded under headings describing the most common symptoms. Those selected were apathy, appetite, thirst, emesis, temperature and pulse rate and character. Particular attention was paid to the degree of hypertension present in the affected cases. At first only a rough estimate was made by digital examination, the pulse being described as full, hard or weak. At a later stage a sphygnomanometer was employed. The small cuff, standard for use in children, proved suitable for use on the dog's fore limb just proximal to the humero-tibial joint. This method was not suitable for very small dogs.

Records were kept on a specially prepared form (Fig. 1). Protocols for each case obtained from these records are contained in Appendices 1 to 6.

BREED:- MONGREL TERRIER AGE:- 1 year SEX:- MALE CASE NO:- 450

Date	13. 4. 49	14. 4. 49	15. 4. 49	16. 4. 49
General Behaviour	NORMAL		NORMAL	
Appetite	GOOD		GOOD	
Thirst	NONE		NONE	
Temperature	100·5 °F		101 °F	
Pulse	140		120	
Blood Pressure	160/100 mm. Hg.			
Agglutination Titre L.C:-	1 : 10,000		1 : 3000	1 : 3000
L.I:-	1 : 100		1 : 300	1 : 1000
Leptospiruria	negative	negative	negative	negative
Urinary pH	6·2	6	7·6	7·6
Proteinuria	+ ve	+ ve	Trace	± ve
Urinary Deposit: Casts: Epithelial				
Large granular				
Small granular	Occasional		Occasional	Occasional
Hyaline				
Terminal				
Cells: Epithelial		Some	Few	Some.
Erythrocytes				
Leucocytes	Several	Several		Several
Blood Urea mgms/100 mls.	20·2	24·4	22·4	40·2
Blood Picture: Haemoglobin %	114	108	100	
R.B.Cs./c.m.m.	7,500,000	6,350,000	6,200,000	
W.B.Cs./c.m.m.	6,000	7,200	12,200	
Differential: Polymorphs N.L. %	12	15	15	
Polymorphs L. %	62	68	71	
Basophils %	0	0	0	
Eosinophils %	4	2	3	
Lymphocytes %	19	13	10	
Monocytes %	3	2	1	
Treatment	100,000 units Sod. Penicillin daily			
Remarks:				

Fig. 1.

Reproduction of record sheet. x $\frac{1}{2}$.

The incidence of Leptospira canicola infection in relation to sex, age and breed of dog affected

Sex incidence

The ratio of males to females of all dogs entering the clinic was found to be three to one and this is borne out by Lauder (1950) who stated that in a similar clinic in Glasgow the ratio was three to one. Table 2 shows that in the present series there were nine males to every one female affected by the disease.

Table 2

Total numbers and percentages of males and females in each of the clinical groups.

Clinical group	Total	Male		Female		Not recorded
		No.	%	No.	%	
Primary-Mild	38	32	91	3	9	3
Primary-Severe	112	90	90	8	10	14
Primary-Most Severe	72	64	91	6	9	8
Secondary-without Uraemia	66	57	95	3	5	9
Secondary-with Uraemia	81	72	91	6	9	9

Age incidence

As shown in Table 3 the incidence of the primary infection

with L. canicola was highest in dogs of one year and under while the secondary stage was found more often in dogs of three to seven years. Full details of the age of dogs in the different groups are given in Appendix 1.

Table 3

Summary of the age distribution detailed in Appendix 1, expressed as a percentage of cases in each group.

Group of Cases	Total in Group	12 months and under	1½, 2 and 2½ yrs.	3-7 yrs.	Over 7 yrs.	Unknown
Primary- Mild	38	51	36	13	0	7
Primary- Severe	112	58	24	18	0	13
Primary- Most Severe	72	39	38	23	0	3
Secondary- - Uraemia	66	8	19	43	30	6
Secondary- + Uraemia	81	13	13	40	34	4

These figures are shown graphically in Fig. 2.

21 pups contracted the disease before they were six months old and 15 cases had entered the secondary renal phase before one year. On the other hand two dogs of seven years and six dogs of five years of age contracted the disease for the first time.

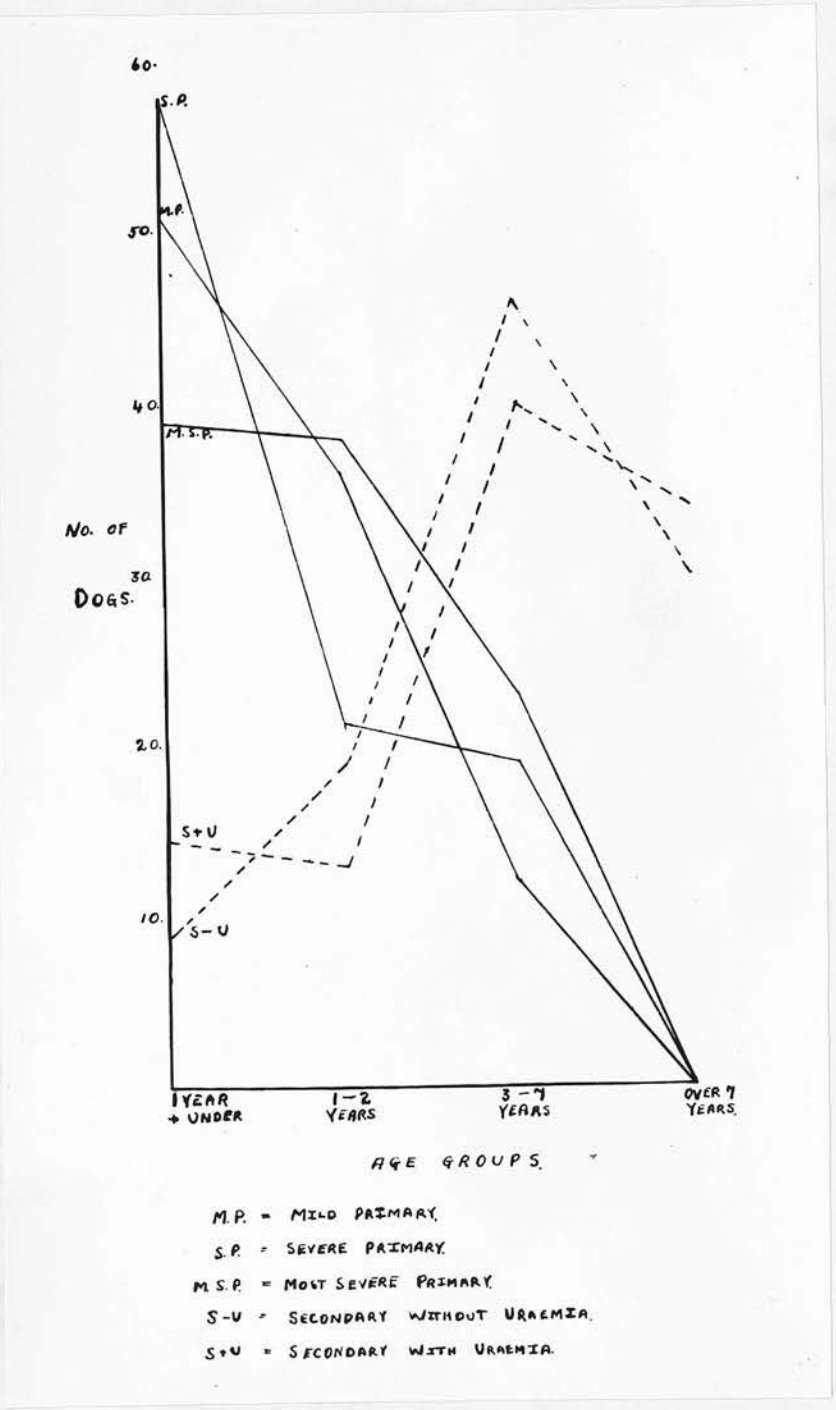

Fig. 2.

The age incidence of the primary and secondary renal stages.

Breed incidence

The numbers of the different breeds which when first examined were in the primary and secondary renal stages together with the total affected are given in Table 4.

Table 4

The distribution of breed incidence.

Breed	Primary cases	Secondary cases	Total
Mongrel Terrier	61	31	92
Collie	19	21	40
Cocker Spaniel	18	19	37
Alsatian	20	12	32
Cairn Terrier	16	7	23
Labrador	8	8	16
Bull Terrier	9	6	15
Mongrel Collie	10	5	15
Smooth Haired Fox Terrier	7	4	11
Scottish Terrier	7	3	10
West Highland Terrier	4	5	9
Border Terrier	6	1	7
Greyhound	4	3	7
Golden Labrador	2	4	6
Rough Haired Fox Terrier	5	1	6
Dalmatian	3	2	5
Springer Spaniel	3	1	4
Welsh Corgi	1	2	3
Airedale	0	2	2
Boxer	1	1	2
Dachshund	2	0	2
Black Labrador	1	1	2
Irish Terrier	2	0	2
Samoyed	0	2	2

In addition to the breeds shown above there was one primary case of each of the following:- Bedlington Terrier, Bulldog, Dandie Dinmont, Mongrel Fox Terrier, Irish Setter, Lakeland Terrier and Mongrel Spaniel. In the secondary renal stage one of each of the following breeds was affected:- Old English Sheep Dog, Pekinese, Sealyham and Shetland Collie. The breed of eight dogs was not recorded.

There were almost twice as many Mongrel Terriers as any other breed, with Collies, Cocker Spaniels and Alsatians being the next most common.

Clinical, serological and biochemical findings

The basis of the classification of clinical cases according to agglutination titres and blood urea levels has already been described in detail (vide supra). A summary is given in Table 5 along with the number of cases in each group.

Table 5

Group	Agglutination Titre	Blood Urea mg./100ml.	No. of Cases
Mild Primary Renal	> 1/10,000 or rising	< 50	38
Severe Primary Renal	> 1/10,000 or rising	50 - 200	112
Most Severe Primary Renal	> 1/10,000 or rising	> 200	72
Secondary Renal without Uraemia	1/30-1/1,000	< 50	66
Secondary Renal with Uraemia	1/30-1/1,000	> 50	81
	No. of Primary cases		222
	No. of Secondary cases		147
		Total	369

Protocols of all 369 cases are given in Appendices 2 to 6.

Bacteraemia

A bacteraemia was demonstrated in seven dogs by recovering

Leptospira canicola in pure culture from the blood. These have been classified in Table 5 as primary cases according to agglutination titres and blood ureas found at subsequent examinations.

Each of these animals showed malaise of varying degree characterised by the sudden onset of a pyrexia associated with apathy and anorexia. Pulse rates were accelerated and on digital examination the pulse felt fuller than normal. Only slight injection of scleral and conjunctival vessels was noticed. Detailed physical examination of thorax and abdomen revealed no further abnormality. In two cases agglutinins against L. canicola were demonstrated at titres of 1/3,000 and 1/10,000 respectively, in the blood sample from which the organism was isolated. At subsequent examinations it was found that agglutinins had developed in the other five cases by the end of two weeks. Nitrogen retention was not evident in any of the cases at this stage. Urine specimens could be obtained from only four of those seven dogs. In one of the urines in addition to the presence of proteinuria and tubular casts leptospirae were demonstrated by dark ground microscopy. Two other urines also had proteinuria and casts but no leptospirae while the fourth was normal.

Blood samples from 51 other dogs showing a pyrexia of

over 104° F. which were submitted to cultural examination all proved to be negative. Only three of these were found to have agglutinating bodies against L. canicola at subsequent examinations and only those three are included in the present series. The others either recovered uneventfully from the initial pyrexia or showed more definite signs of distemper on subsequent examinations. Three cases of salmonellosis were detected.

Primary renal stage

Clinical signs. The 38 primary cases described as mild were submitted by their owners for examination because of a mild malaise, excessive thirst and polyuria or nocturnal incontinence. Physical examination of these frequently revealed no abnormality other than a pulse somewhat full in volume.

On the other hand the 112 cases classified as severe primary were obviously ill and persistently apathetic and anorexic. Excessive thirst was a constant symptom in those cases often being accompanied by emesis of varying frequency. Polyuria was commonly present but a varying degree of oliguria was found when vomiting was frequent. The mouth often had a bad odour and the tongue often had a brownish tinge. In no case was pyrexia recorded. The pulse was markedly increased in volume and sometimes in rate. Icterus was

present in two cases only.

The most severe cases were characterised by repeated drinking and vomiting of water. Movement was made unwillingly and when standing the back was held arched in a most pained looking posture (Figs. 3, 4, 5 and 6). These dogs were completely apathetic and usually evinced no interest in food or their surroundings. Some owners stated that the illness had been of short duration, others that the condition had gradually deteriorated over seven to 10 days. Sometimes there was a history of a few days malaise having occurred a week or two earlier. The foetid odour of the breath was most repugnant and it was frequently accompanied by ulceration of the buccal mucosa and lingual border. In two dogs necrosis of the border of the tongue had developed to such an extent that sloughing was about to take place. As in the less severe group no case of pyrexia was found. The pulse volume was full but became rapidly weak with the onset of death. Occasionally an enlarged left kidney was palpable. 70% of the dogs in this group did not recover from the disease.

Leptospiruria and agglutination titres. In Tables 6, 7 and 8 are summaries of the agglutination titres against L. canicola found in each of the mild, severe and most severe groups along with the numbers having leptospiruria.

Fig. 3. Most severe primary case. Mongrel Retriever. Case 445.

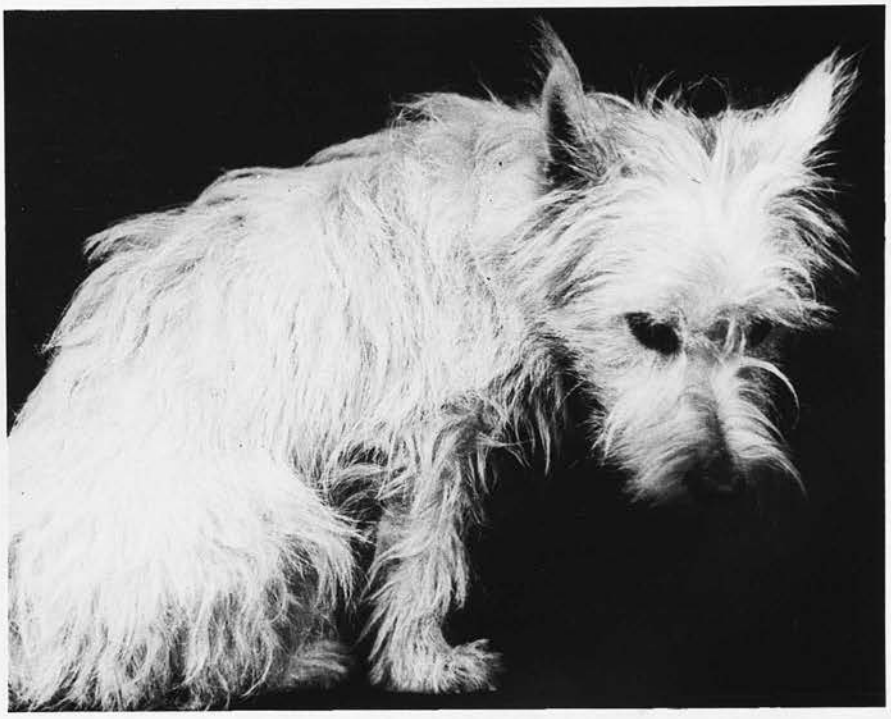

Fig. 4. Most severe primary case. West Highland Terrier. Case 212.

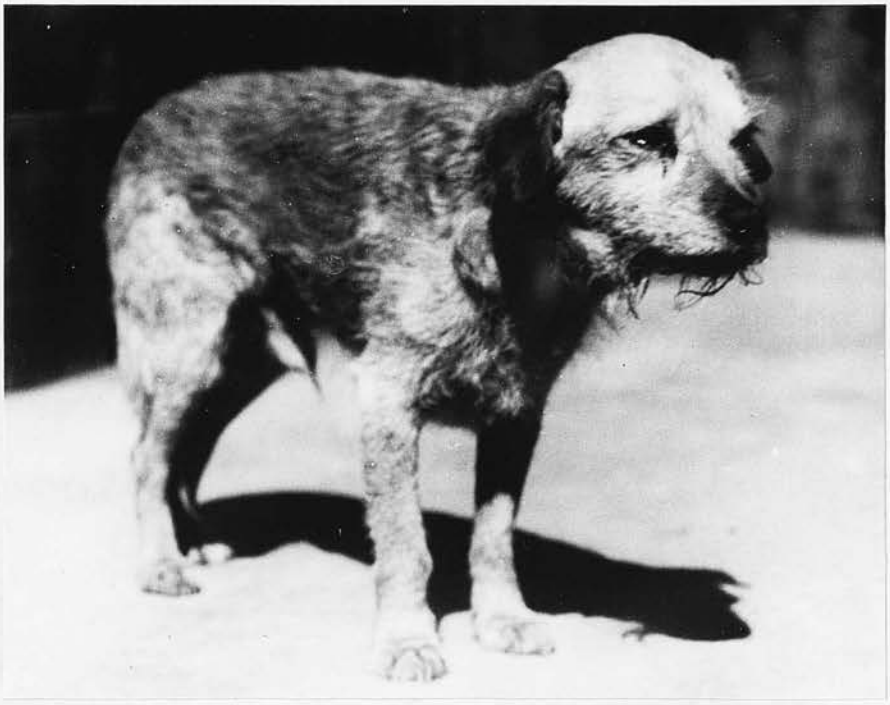

Fig. 5. Most severe primary case. Border Terrier. Case 535.

Fig. 6. Most severe primary case. Mongrel Collie. Case 487.

Table 6

Agglutination titres of dogs in the mild primary renal group when first examined compared with the incidence of leptospiruria.

Titre	No. of Cases	No. of urines examined	No. having leptospiruria	% having leptospiruria
1:3,000	12	10	3	30
1:10,000	15	15	8	53
1:30,000	10	9	7	78
Total	37	34	18	53

Table 7

Agglutination titres of dogs in the severe primary renal group when first examined compared with the incidence of leptospiruria.

Titre	No. of Cases	No. of urines examined	No. having leptospiruria	% having leptospiruria
1:3,000	16	16	3	19
1:10,000	52	50	37	74
1:30,000	43	40	30	75
Total	112	106	70	66

Table 8

Agglutination titres of dogs in the most severe primary renal group when first examined compared with the incidence of leptospiruria.

Titre	No. of Cases	No. of urines examined	No. having leptospiruria	% having leptospiruria
1:3,000	9	8	2	25
1:10,000	28	27	13	49
1:30,000	35	33	18	55
Total	72	68	33	49

It can be seen that in each group the higher the agglutination titre the greater was the number of cases having leptospiruria. In most cases the agglutination titre had begun to fall by the end of two months and had reached a level of 1/1,000 or less at the end of six months.

Proteinuria. Samples of urine from 138 dogs were examined for protein. It was present in all cases in varying quantities and usually accompanied by tubular casts (Figs. 7, 8, 9, 10 and 11). The number of casts varied greatly. In some of the most severe cases large numbers were observed (Fig. 7) while others had only a few. The majority of the milder cases had comparatively few casts in the urine.

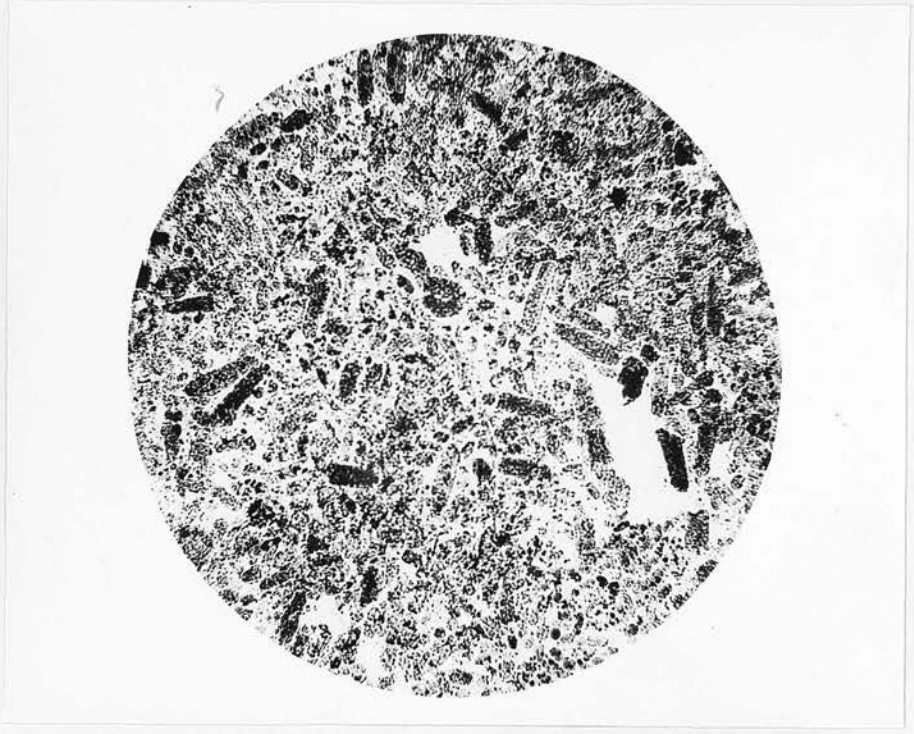

Fig. 7. Granular tubular casts. Most severe primary stage. x 110.

Fig. 8. Epithelial and granular casts. Most severe primary renal stage. x 110.

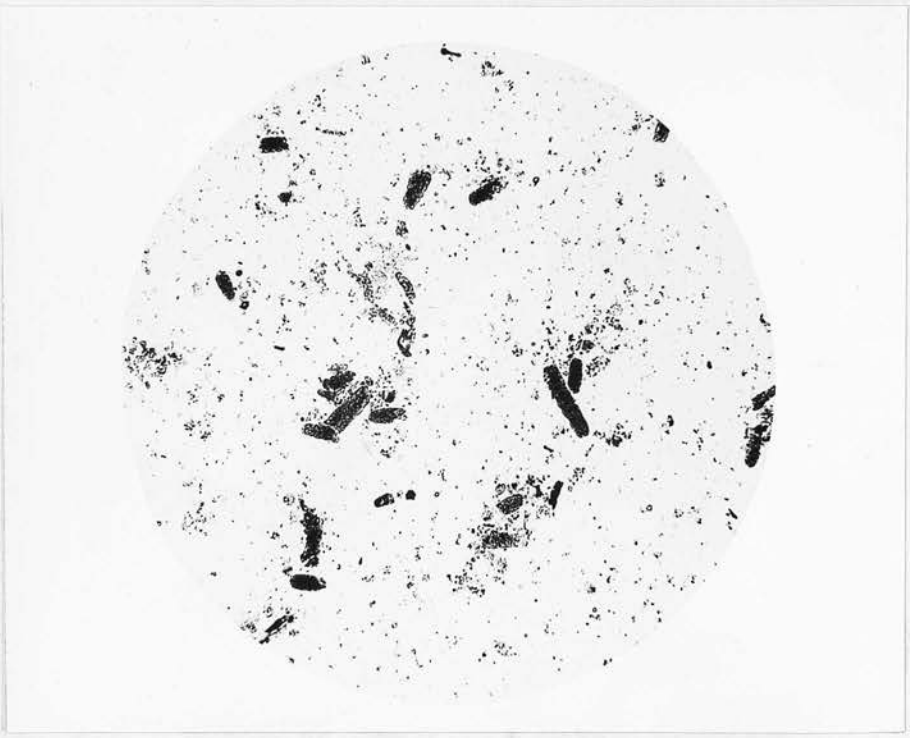

Fig. 9. Granular casts. Severe primary stage. x 110.

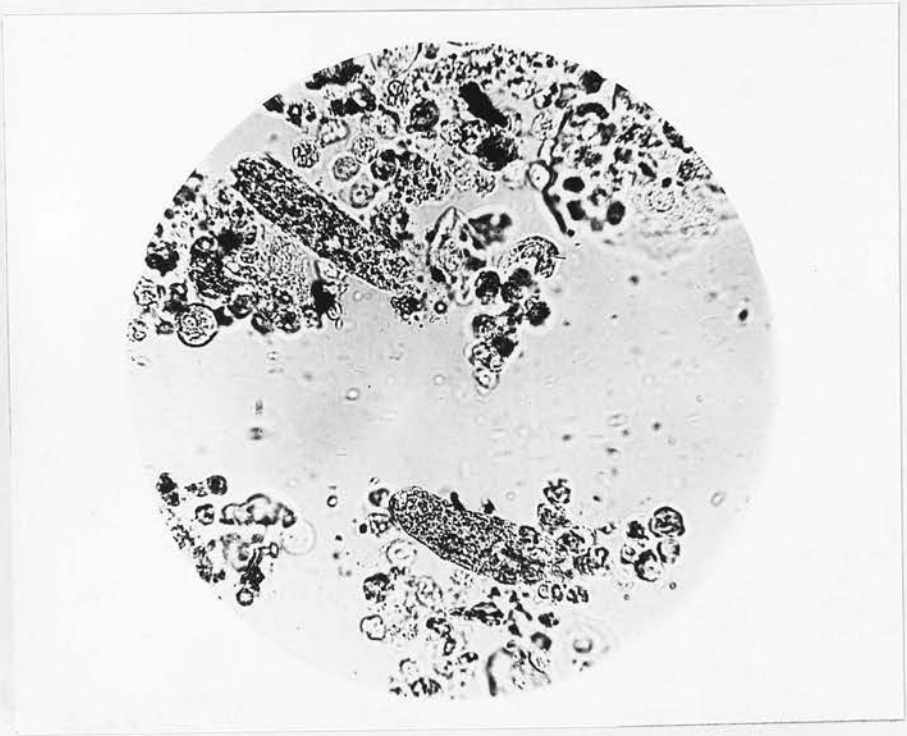

Fig. 10. Granular casts. x 410.

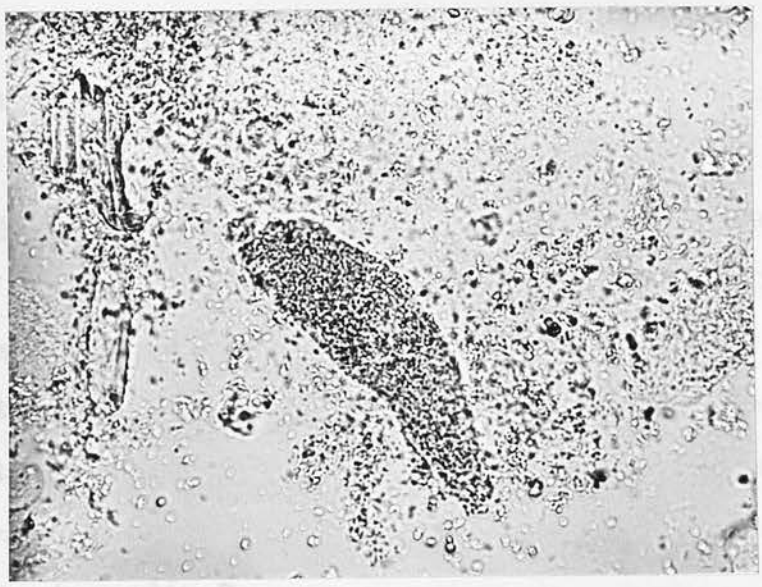

Fig. 11. Granular cast. x 410.

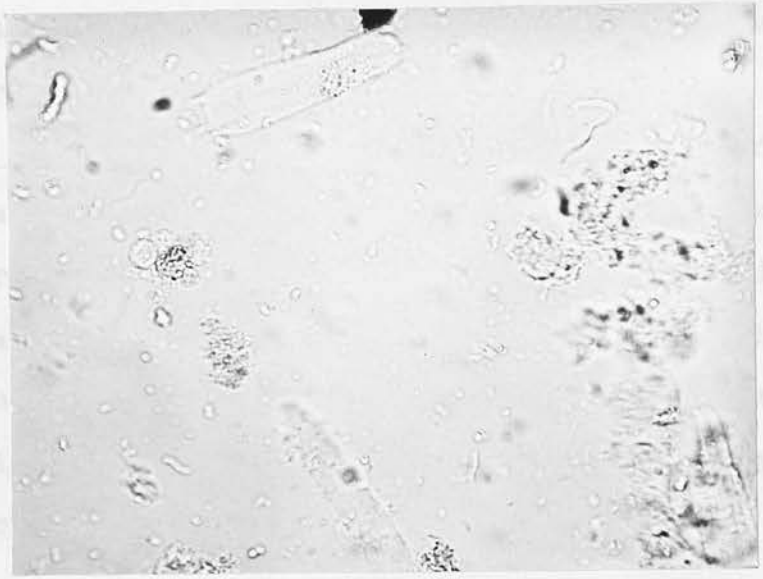

Fig. 12. Hyaline casts. x 410.

Usually the casts were granular in nature but occasionally epithelial forms were noted.

Leucocytosis. The blood leucocytes were enumerated in 66 primary cases. Of these 36 (55.5%) reached a figure greater than the upward standard deviation given by Mayerson (1930) (cited by Boddie 1944). Differential leucocyte counts carried out on the 66 cases showed that 60 (91%) had 10% or more of nonlobulated neutrophils. Details of leucocyte counts are given in Appendix 7.

Anaemia. In five of 25 (20%) cases in the most severe primary group and in two of 25 (8%) cases in the severe primary group there was a marked anaemia, erythrocyte counts being as low as 3,500,000/c.mm. and haemoglobin concentration as low as 7 gm./100 ml. No change was noted in the thirteen mild primary cases examined. Details of the erythrocyte examinations carried out are given in Appendix 8.

Blood urea levels. As already described blood urea levels have been used as a basis for dividing the primary cases into mild, severe and most severe. Apart from an occasional case which had a high blood urea and yet showed little physical upset the blood urea level of a dog accurately reflected its general clinical condition. Thus it was invariably used as an aid to prognosis.

Evidence of this correlation between blood urea level and the severity of the animal's condition is gained from a study of the mortality figures in Table 9.

Table 9

Group	Blood Urea mg./100 ml.	No. of cases	No. of deaths from renal failure	Mortality %
Mild	50	38	0	0
Severe	50-200	112	9	8
Most Severe	200	72	51	71

Because of the danger of infection to humans all dogs with leptospiruria were admitted to the Veterinary Hospital for therapy. Most of the animals were treated with either the sodium or procaine salts of penicillin. The mild and severe cases showed a marked improvement within a few days but over 71% of the most severely affected cases died. Those which recovered under therapy ceased to shed leptospirae after two or three days and the blood urea levels fell to normal within two weeks. Agglutination titres against L. canicola persisted as did the excretion of protein and tubular casts in the urine.

Secondary renal stage

When first examined 147 dogs were found to have chronic nephritis associated with the persistence of agglutinating antibodies against L. canicola. These cases have been divided into groups, one having nitrogen retention and the other blood urea levels below 50 mg./100 ml.

Clinical signs. Some of the 66 dogs without nitrogen retention were presented for examination because of some other ailment, and the presence of a renal lesion associated with persistent agglutinins was detected only because of routine blood and urine examinations. In other dogs there was a gradual loss of weight accompanied by thirst and polyuria. Occasional vomiting took place often in the early morning.

The 81 cases with nitrogen retention when first examined all showed fairly typical symptoms. Anorexia was usually complete and vomiting frequent. The vomit was often blood-stained and occasionally consisted almost entirely of blood. The dogs were very thirsty and had been losing weight for some time. Two dogs took epileptiform convulsions in the terminal uraemic phase. The breath had a foetid odour usually accompanied by buccal and lingual ulceration similar to that seen in the primary stage. In some cases there was necrosis of the tip of the tongue. On auscultation of the heart a systolic

murmur was frequently heard. The pulse left hard. The impression that was gained on palpating this type of pulse was that the force behind the pulse wave had been increased while the arterial wall had lost much of its elasticity. This was substantiated by the marked degree of left ventricular hypertrophy found at autopsy. The last few hours of life were characterised by a rapid weakening of the pulse accompanied by hyperpnoea and prostration.

Agglutination titres. All cases in the secondary renal stage had agglutination titres of 1/30 to 1/1,000 against L. canicola most of them being either 1/100 or 1/300.

Leptospiruria. No leptospirae were found in any of the 78 urines examined. Ten of those urines were centrifuged at 6,000 revolutions per minute for half an hour and the deposit examined carefully for leptospirae without finding any organism.

Proteinuria. In all of 78 secondary cases in which the urine was examined there was proteinuria varying in amount from a mere trace to as much as 7 gm./24 hour volume. In contrast to primary cases hyaline casts (Fig. 12) were found in the centrifuged deposit but small finely granular casts were also present. Sometimes the hyaline casts contained a few granules.

Anaemia. Haematological examination revealed that in

16 of 28 secondary cases with uraemia there was an anaemia whereas none of 18 cases examined with secondary lesions but no nitrogen retention was anaemic. Details of the examinations carried out are given in Appendix 8.

Blood urea levels. 57 of 81 (70%) cases with blood urea levels of over 50 mg./100 ml. were known to have died; others probably did so but were not examined again. Once nitrogen retention had developed in the secondary stage most of the dogs died within a few days or weeks. With much care it proved possible to keep an occasional dog alive for several months with a blood urea level of more than 100 mg./100 ml. Therapy consisted of enforced rest in a kennel, a diet low in protein with access to as much water as the dog could take without vomiting, and a short course of penicillin therapy. This palliative treatment was helpful in only a small number of cases with uraemia and even then for only a short time, but it did appear to produce an improvement in secondary cases without uraemia which were showing intermittent malaise.

Transition from primary to secondary renal stage

In addition to the information concerning the secondary stage gained from the 147 cases described above, it proved possible to follow 46 primary cases into the secondary stage over periods varying from six months to four years. The owners of those dogs took them back to the clinic from time to time for further examination. In Table 9a are shown the various periods during which those animals were observed.

Table 9a

Period of time under observation. Years	No. of dogs
½ - 1	6
1 - 2	12
2 - 3	9
3 - 4	15
4	4
Total	46

Six of those cases died of renal failure in the secondary stage five months to two years after the primary infection. The others were apparently well when last examined and according to their owners were lively and ate well. Some of them became

thirsty intermittently. Clinical examination revealed early cataract of the lens in four cases. Five had a slight systolic murmur and the pulse of each felt hard to a varying degree. Blood pressure readings recorded in Table 9b show that there was a rise above the normal (130/90 mm. Hg. systolic/diastolic) in all but one case.

Table 9b

Case No.	Age Years	Time from initial infection Years	Blood pressure mm. Hg. Systolic	Diastolic
52	7	4	180	40
64	6½	4	160	90
104	4¾	4	210	160
168	9	4	150	90
179	5½	3¾	170	90
247	6	3½	240	140
250	7	3½	230	140
276	5½	3½	180	80
318	4½	3½	190	110
324	6¼	3¼	210	40
399	5½	3	150	80
501	3	2	110	70
520	7	2	190	120
A8	4½	1½	180	140
A50	3¾	1¼	280	180
A648	4	½	190	120

All 46 dogs in this group had two features in common, persistent agglutinins against L. canicola and proteinuria frequently accompanied by tubular casts. The titres varied from 1/100 to 1/1,000. The amount of protein varied from a trace to as much as 200 mg./100 ml. urine. The casts were

predominantly hyaline with a few granules but there were usually some granular casts present.

Section 2.

The pathology of the disease in the dog associated with naturally occurring infection by Leptospira canicola.

Historical

The renal lesions in the dog which are about to be described as being associated with infections of Leptospira canicola appear to have been familiar to pathologists in Europe as long ago as 1899 although they did not regard them as being part of a spirochaetal disease.

Unfortunately, the original articles of these authors are not available but Hyhlik quotes Albrecht (1899), Hutyra and Marek (undated) and Szchokke (1900). Hutyra apparently described renal haemorrhages, capillary congestion and nodular interstitial leucocytic infiltration associated with degeneration of tubular epithelium and detachment of the epithelium of Bowman's capsule. All three writers appear to have classified the renal lesions according to the relative predominance of interstitial, tubular and glomerular involvement and to have agreed that the most characteristic finding was a nodular mononuclear cell infiltration compressing the tubules. They regarded the condition as acute interstitial

nephritis of lymphocytic and plasma cell type.

It was not until over 20 years had elapsed that in 1924 spirochaetes were described along with similar renal lesions. In that year Lukes, Hyhlik and Krivacek all working in Lukes' department described in some detail the lesions of a number of cases showing spirochaetes in the kidneys. The most detailed description of the material for autopsy is provided in a separate paper by Hyhlik which is based on the examination of 22 cases. He describes ulcerative and necrotic lesions in the mouth, oedematous and haemorrhagic gastrointestinal mucosae and hyperaemic liver and kidneys. The kidneys showed greyish-yellow areas of infiltration of the cortex and subcapsular haemorrhages. Microscopically, the renal lesions consisted of mononuclear cells, mainly lymphocytes and plasma cells. There were very few polymorphonuclear leucocytes. This worker also reported that in five of the dogs there were cellular inflammatory nodules deep in the media of the large vessels, the pulmonary artery being affected more often than the aorta.

Krivacek (1924) stated that he had found spirochaetes in 17 of 21 dogs examined after death from Stuttgart disease. In the kidneys they were found most frequently in the convoluted tubules where they were intra- and extra-cellular. Sometimes a clump of spirochaetes appeared to fill the tubular

lumen while in others they appeared as distinct spiral organisms. Krivacek also noticed that the spirochaetes were usually in the convoluted tubules and never in the glomeruli or other parts of the nephrons although he did observe them in casts of the collecting system. It is also interesting to note that he described spirochaetes in the walls of the large vessels and also in spleen, liver and pancreas in a proportion of his cases.

In 1925 Lukes published a larger series of cases in which he identified spirochaetes in 97 of 105 fatal cases of Stuttgart disease. He also described them as being present in the convoluted tubules near the glomeruli and occurring as single organisms or in clumps. He described the cellular exudative process as an acute interstitial nephritis with a predominantly mononuclear infiltration of focal distribution. There were few spirochaetes to be seen in the cellular exudate although the nearby convoluted tubules contained them. He also cited Schramek (without reference) who described a lymphocytic interstitial nephritis in 15 protracted chronic cases. Schramek also noted cellular granulomatous nodules on the intercostal and diaphragmatic pleura and on the endocardium. In the aorta and pulmonary arteries he recorded granulomatous destruction of the elastica which resembled those of syphilis in the human subject.

In another paper (1925) Lukes, Jelinek and Schramek discussed the relationship of Stuttgart disease to chronic nephritis in the dog. They gave accounts of the pathological changes in six young dogs under the age of five years which had survived acute attacks of Stuttgart disease and later developed chronic nephritis. All had ulcerative stomatitis, haemorrhagic gastric or intestinal lesions with granular contracted kidneys. One of those dogs also had chronic endocarditis. In four of these cases the nephritis described was of subacute type with persistent round cell infiltration of the interstitial tissue. In the remaining two dogs the renal lesions had progressed to marked sclerosis. Spirochaetes were difficult to find although more numerous in the subacute cases in which they were observed mainly in the convoluted tubules. Unfortunately no details are given of the time which had elapsed since the primary attack of the disease. It is of very considerable interest to note that in the year 1925 those workers were recognising spirochaetes in the tubules of dogs with advanced chronic nephritis. All of this work emanating from Lukes' department appears to have been of the highest order. The only doubt that can be cast on it is that concerning the nature of the organism. Was this spirochaete the same as the strain of Leptospira which Klarenbeek and Schuffner

isolated in 1933 and called L. canicola and has been isolated by many others since? The extraordinary similarity of the clinical signs and the renal histopathology seem to indicate clearly that the Stuttgart disease of those earlier years was indeed caused by Leptospira canicola.

Another excellent piece of work of comparative interest to the present thesis was that published by Henschen (1924) in Joest's Spezielle pathologische anatomie der Haustiere. He regarded interstitial lymphocytic nephritis as the most frequent and important inflammatory condition of the canine kidney. He emphasised that the infiltration in the acute stage might be diffuse or nodular and that the latter was the more common. He noted, too, that in the nodular form, the deep part of the cortex and the external part of the medulla were involved most frequently. The infiltration was often pronouncedly peri-glomerular but neither the glomeruli nor the tubules themselves showed changes. To Henschen the tubules themselves appeared to pass unaltered through the exudate. Most of the cells were of the lymphocytic series; polymorphonuclear leucocytes were seldom numerous except in rare instances when the centres of the nodules were almost purulent. Henschen recognised subacute and chronic stages of this infection and described them in some detail particularly with reference to their

separation from the coarse, less regular fibrosis of infarction and of pyelonephritis. Microscopically, too, he noted the absence of epithelial crescents in Bowman's capsule and thus contrasted the condition with chronic glomerulonephritis. He also mentioned the tendency in older dogs to acute and subacute exacerbation of the chronic stage and of the establishment of a persistent subacute stage. This excellent description and evidence of progression and exacerbation is rendered all the more remarkable as Henschen did not know of the leptospiral etiology and associated the condition with distemper and pneumonia.

Wirth and Klarenbeek did not describe the histopathology of the disease in any detail apart from the localisation of spirochaetes and it was not until 1941 that another account of the renal lesions was forthcoming. In that year in America Bloom gave a description based on nine cases. As five of the dogs had had icteric illnesses and four non-icteric illnesses and as agglutination tests were performed in life on only three icteric cases and these were inconclusive, it is impossible to say that he was describing cases caused by L. canicola. Bloom emphasised that interstitial nephritis is the predominant renal inflammatory disease of the dog and is met with in a wide variety of infections. He also believed that recovered cases of

Leptospiral nephritis might provide the source of cases of chronic interstitial nephritis. It is interesting to note that he recorded atypical regenerated epithelium in the renal tubules as being present in all the nine cases examined. In these tubules nuclear mitotic figures were numerous and the proliferative activity was such that the cells frequently assumed a giant-cell-like appearance.

In 1948 two case reports were published by Jennings in conjunction with Mills. These were cases which had been diagnosed clinically and serologically as primary cases of Leptospirosis canicola. One dog was 19 months old, the other five years. In the first case there appeared to be a chronic nephritis on which had been superimposed an acute process characterised by marked congestion of the blood vessels, tubular degeneration and only a few areas of cellular infiltration mainly in the cortex and consisting of plasma cells. This description is not what would be expected from the course of the disease as described by Mills. In the second case, in addition to the above changes there was observed a marked focal cellular infiltration throughout the cortex. Jennings states these cells were largely epithelioid in type with only a few plasma cells and lymphocytes. Neutrophils were sparse.

In 1949 Montgomery, discussing the work of McIntyre and

Stuart, gave a brief description of the renal lesion. In the primary cases he had found an acute focal or diffuse interstitial nephritis characterised by an infiltration of non-granular leucocytes sometimes of remarkable intensity. By contrast the glomeruli were singularly unaffected but a varying degree of degeneration and necrosis of tubule cells was often present. In the secondary cases he stated interstitial fibtosis to be the outstanding lesion. In some kidneys glomerular atrophy and fibrosis occurred usually in association with muscular hypertrophy of renal arteries and arterioles and these changes appeared to be a reaction to hypertension.

This preliminary statement was substantiated later (1952) in a paper by McIntyre and Montgomery in which were described in detail the renal lesions of canine leptospirosis canicola.

In 1951 and 1952 Platt described renal lesions in dogs which had many features in common with those described by McIntyre and Montgomery but he had no knowledge of their illness during life or of their serological reactions to leptospira. He did not discern any spirochaetes in those kidneys examined.

In 1945 Jones seized an opportunity presented to him by the United States Army Veterinary Corps of examining the kidneys from 40 dogs which were not showing any physical abnormality

but which reacted positively to a macroscopic agglutination test for Leptospira canicola. In these kidneys he described focal interstitial lesions with discernable spirochaetes in only six of them.

In 1953 Monlux extended this survey of renal lesions to 321 cases. The material for this survey was obtained from the pathology department of the Armed Forces Institute. Unfortunately clinical histories are missing from this account. He describes 283 of the cases as showing primarily interstitial lesions and the others as inflammatory vascular diseases. Spirochaetes were demonstrated in 40 of this number, 22 being acute cases characterised by periglomerular, perivascular and intertubular infiltrations of lymphocytes, plasma cells, monocytes, reticuloendothelial cells with only a few neutrophils. This infiltration was characteristically more extensive at the cortico-medullary junction. 83 cases of chronic interstitial nephritis were described in this series. Monlux stated the most remarkable changes were in the outer zone of the medulla where connective tissue and cellular infiltrates surrounded extremely hyperplastic tubules often forming large cystic spaces filled with eosinophilic hyaline casts. Partial replacement of the cortical parenchyma by connective tissue resulting in atrophy, collapse and obliteration of tubules and

glomeruli was also noted. Thickening of the blood vessels was noted. Monlux describes the hyaline changes in the glomeruli as secondary amyloidosis and makes no attempt to link this with arterial thickening as part of a hypertensive syndrome. He concludes that advanced cases of chronic nephritis were not due to leptospirosis largely because he failed to demonstrate argentophilic leptospires.

Materials and Methods

Of the 369 dogs included in this series 149 are known to have died or to have been destroyed in extremis between October 1947 and November 1951. Of these 117 died of renal failure, the others from intercurrent disease such as distemper. Of the 149 cases 82 were available for post mortem examination. Destruction was carried out by the intravenous injection of nembutal. Autopsy was performed within the first few hours after death. In addition to noting changes in the kidneys examination was made for other lesions. Representative portions of kidneys were fixed in 10% neutral formalin and in formol perchloride solutions. Paraffin sections were stained by a variety of methods including haematoxylin and eosin, Weigert's elastic tissue stain and Masson's trichrome methods. Levaditi's original method was used for demonstrating leptospirae. A microscopic study of the renal lesions was carried out including a search for spirochaetes in the Levaditi sections.

Autopsy of dogs which died in the primary renal stage

Oral necrosis was often well established particularly at the border of the tongue and on the buccal surface opposite the canine and carnassial teeth. On two occasions the tip of the tongue was about to slough off. In the cases which had died in uraemia or were moribund when destroyed there was often extensive haemorrhage into the stomach and small intestine, the respective mucosae being congested over a great area. Crumbling or ulcerative endocardial lesions (Fig. 15) were present in 22 of 43 (50%) primary cases. These friable masses tended to involve the endocardium at the base of the valves rather than the cusps. In one case similar lesions were found in the thoracic aorta.

In cases which died during the primary renal stage of intercurrent disease such as the nervous complications of distemper, no naked eye lesions were apparent in the kidneys.

Renal lesions. The kidneys were swollen and sometimes pale in colour. The appearance of the cut surface presented either a diffuse greyish mottling effect throughout the cortex or a broad yellowish-white band in the cortico-medullary boundary zone with a few scattered grey foci throughout the cortex (Figs. 13 and 14). On examination with a hand lens this band resolved itself into an aggregation of nodules similar to

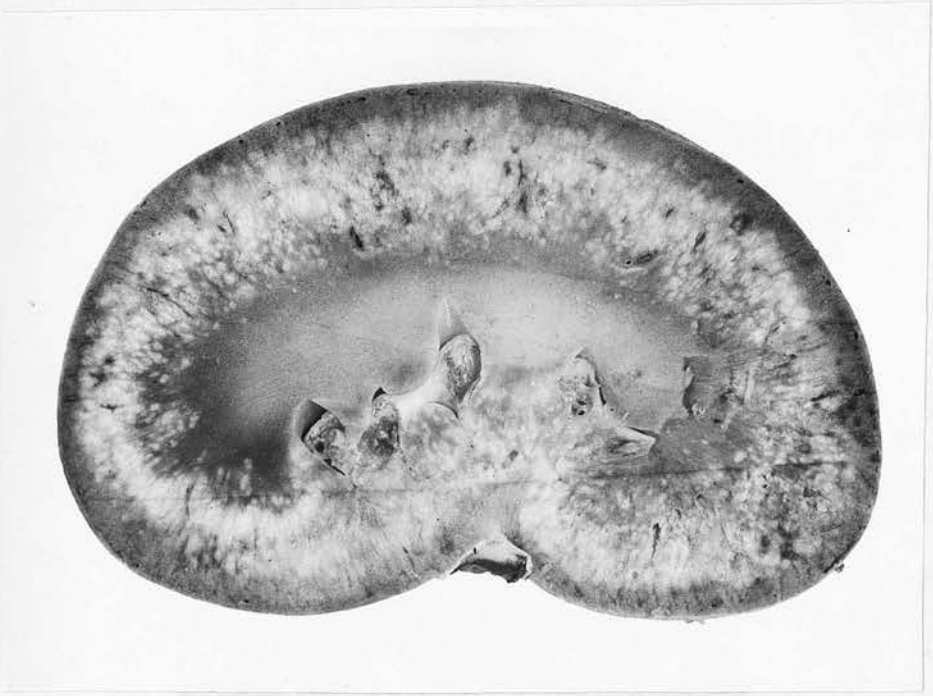

Fig. 13. Primary renal stage. Cortical infiltration and nodules at boundary zone. Case 487. x $1\frac{1}{2}$.

Fig. 14. Primary renal stage. Cortical and boundary zone nodules. Case 481. x $1\frac{1}{2}$.

Fig. 15. Primary renal stage. Acute endocarditis. Case 574. x $2\frac{1}{2}$.

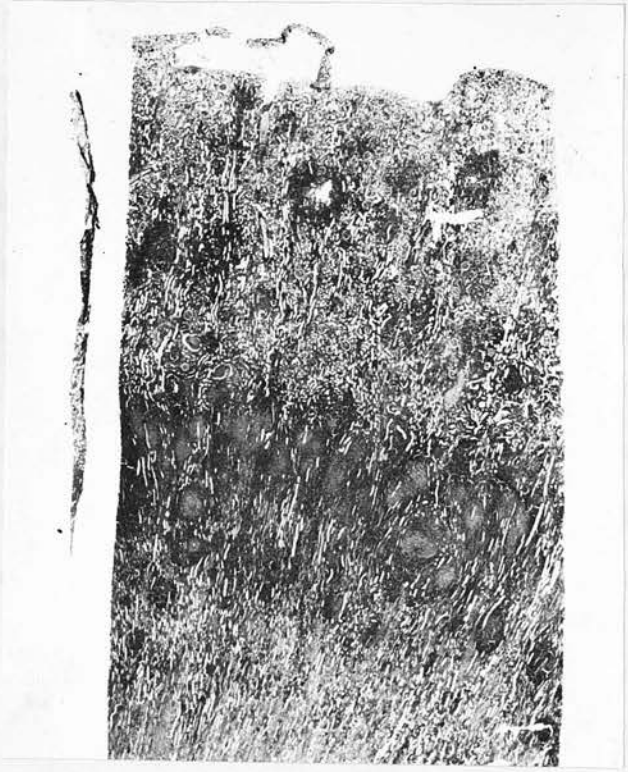

Fig. 16. Primary renal stage. Infiltration of boundary zone. Case 228. H. and E. x 11.

those in the cortex. There was no naked eye evidence of infiltration of the medulla. Haemorrhages were occasionally seen below the capsule.

On microscopical examination the cortico-medullary band consists of an intense cellular infiltration, nodular in character (Fig. 16). The scattered foci throughout the cortex are similar. Sometimes irregular masses of these foci appear in the cortex. The medulla is only occasionally involved. The cellular infiltration (Figs. 16a, 16b, 17) consists largely of lymphocytes and plasma cells but mononuclear leucocytes and histiocytes also occur. Sometimes small collections of neutrophil polymorphonuclear leucocytes are apparent at the centre of the nodules and there are sometimes scattered single polymorphs throughout the inflammatory zone. The glomeruli appear almost normal apart from a small amount of exudate in the capsular space. The tubules often become completely occluded by the infiltration. Cloudy swelling and necrosis of tubular cells are common in infiltrated areas. Within the lumen of some of the tubules there are casts and small plugs of inflammatory cells. Leptospirae are usually abundant in the convoluted tubules and may be found singly or in clumps (Figs. 18a, 18b). No organisms are distinguishable in the cellular masses although numerous argentophilic granules are often present. Capillary

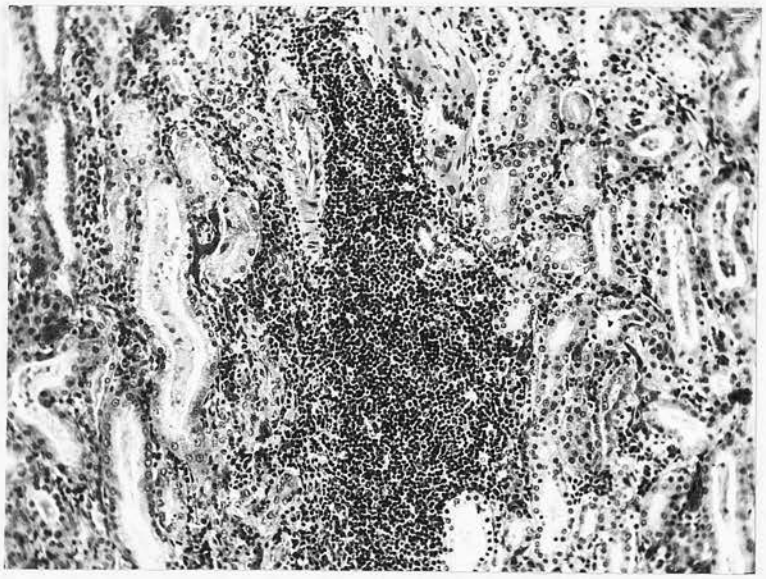

Fig. 16a. Primary renal stage. Cellular infiltration.
Case 422. H. and E. x 110.

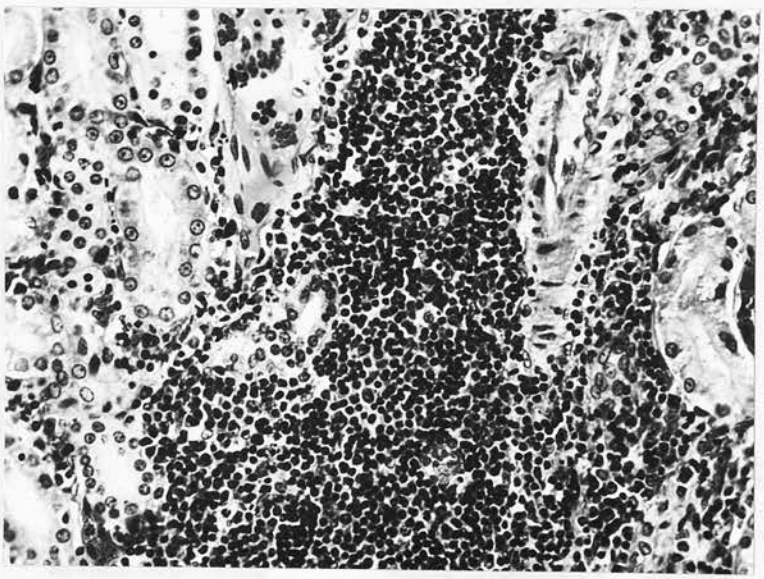

Fig. 16b. Primary renal stage. Cellular infiltration.
Case 422. H. and E. x 375.

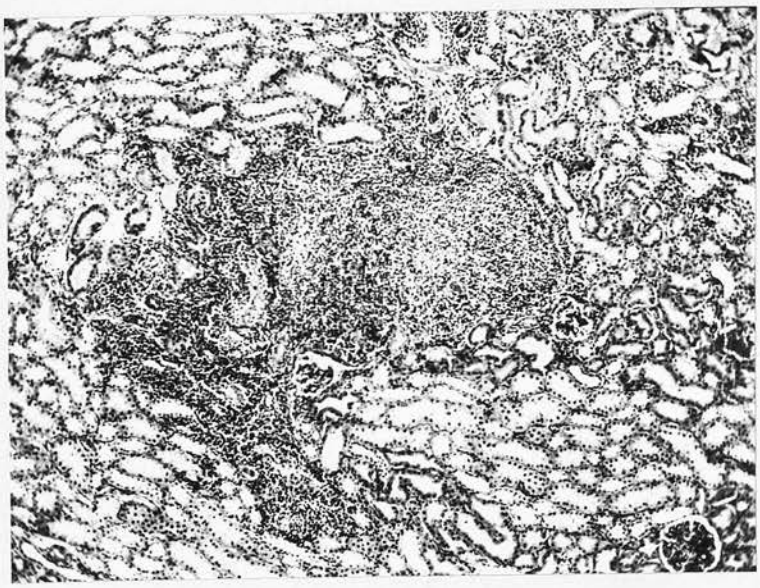

Fig. 17. Primary renal stage. Nodular infiltration. tubules. Case 228. H. and E. x 100.

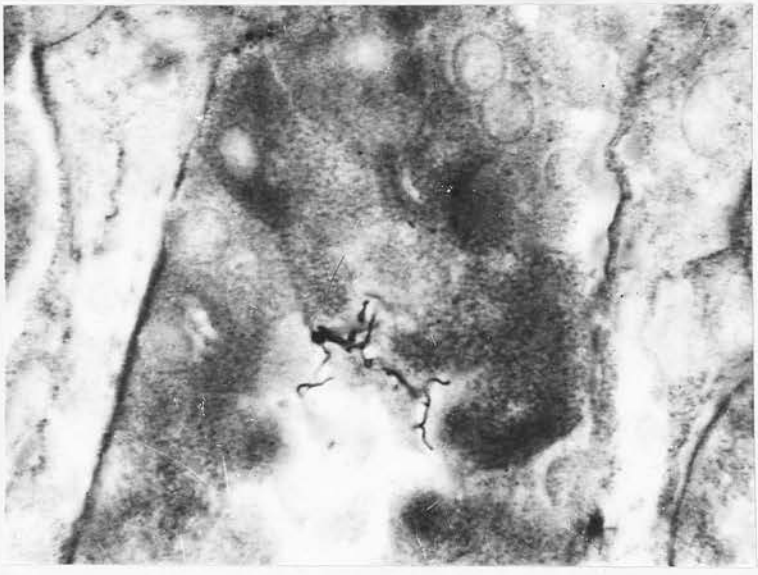

Fig. 18. Acute renal stage. Leptospirae in convoluted tubule. Case 228. Levaditi. x 340.

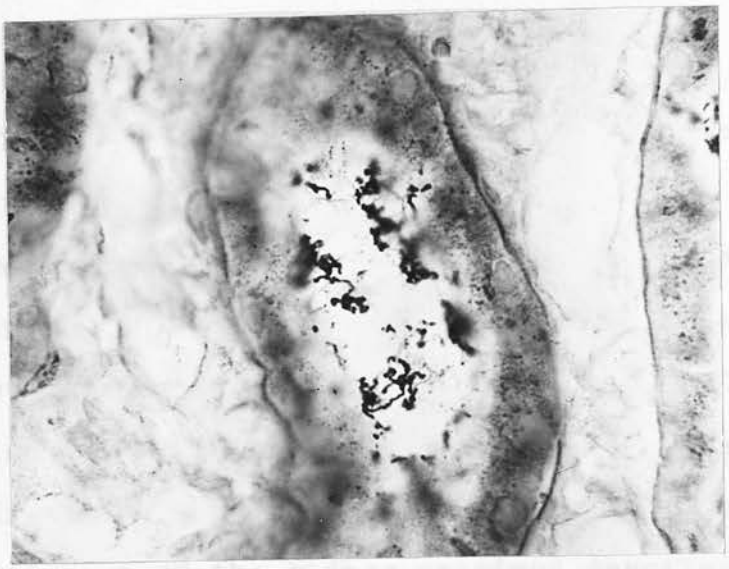

Fig. 18a. Primary renal stage. Leptospirae in tubules. Case 422. Levaditi. x 480.

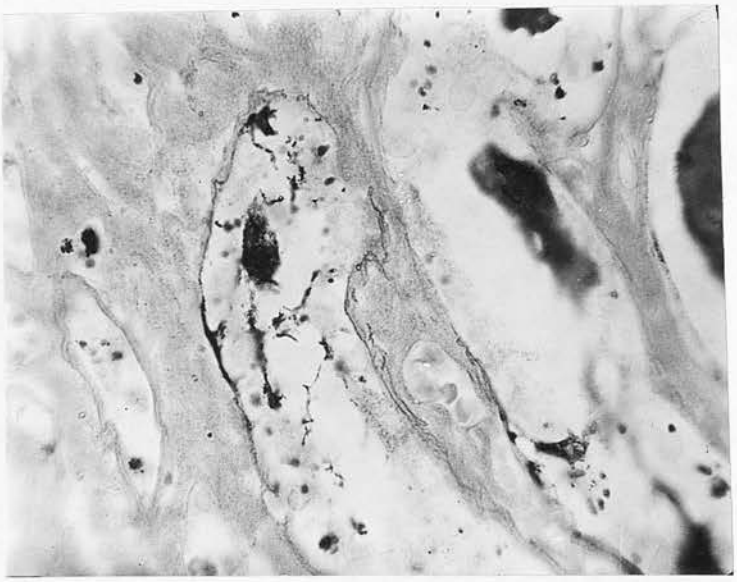

Fig. 18b. Primary renal stage. Leptospirae in tubules. Case 224. Levaditi. x 480.

blood vessels are seen in the nodules but they are not numerous, the nodules being relatively avascular. The above description is based on the most severely affected cases which died of renal failure. The cases which died of intercurrent disease without having nitrogen retention and were available for autopsy show only small focal lesions consisting of lymphocytes and plasma cells. Little or no damage to nephrons can be seen. Indeed, one case, No. 270, had no recognisable lesion in that part of the kidney examined despite the presence of agglutinins in the blood. These mild cases are of particular interest when compared with the slight lesions which resulted in many pups experimentally infected.

Autopsy of dogs which died in the secondary renal stage

In the cases which died in terminal uraemia there were mouth lesions similar to those seen in acute cases with uraemia. Ulceration occurred chiefly at the border of the tongue and on the buccal surfaces chiefly opposite the larger teeth. In several cases there was necrosis of the tip of the tongue. A number of cases had bilateral cataract of the lens. Gastro-intestinal haemorrhage occurred similar in extent to that observed in acute cases. There was a pronounced hypertrophy of the left ventricle (Fig. 19) sometimes the wall being four and five times as thick as that of the right. In 20 of 39 (51%) secondary cases autopsied small whitish nodules were observed along the border of the cusps of the atrioventricular valves and in some of these there was shortening of the chordae tendinae. These lesions were always present in those cases which had had a systolic murmur when examined clinically. But nodules were also present even in those cases in which no murmur had been detected.

Renal lesions. The kidneys were pale and contracted in appearance, sometimes only half their normal size. The surface was finely granular because of numerous shallow depressions which were quite deep in a few cases. The cut surface revealed a very narrow cortex, the calyces being thinned irregularly in

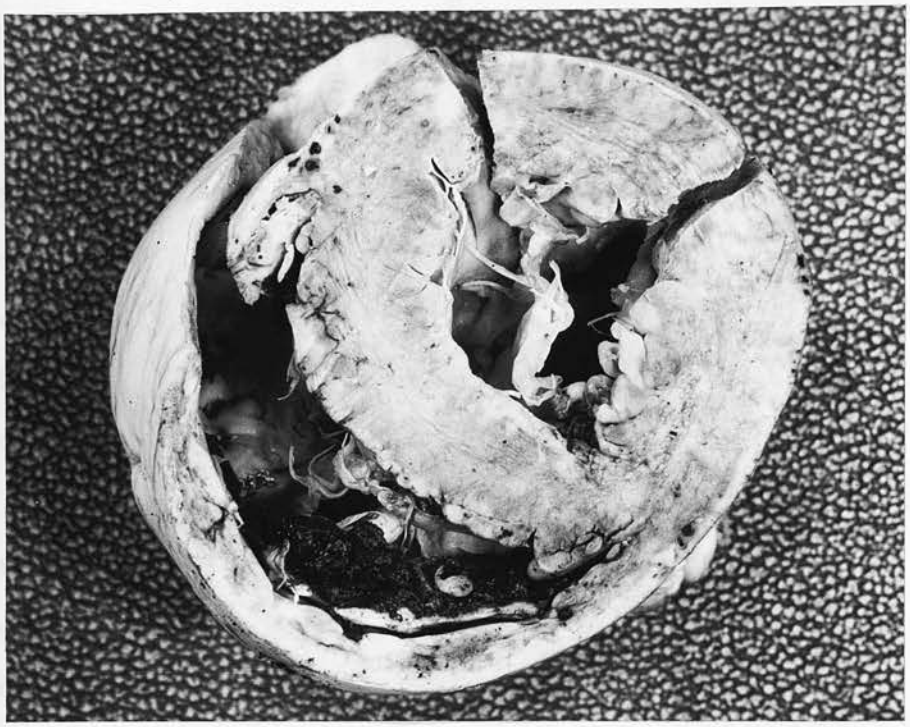

Fig. 19. Secondary renal stage. Left ventricular hypertrophy. Case 171. x $1\frac{1}{2}$.

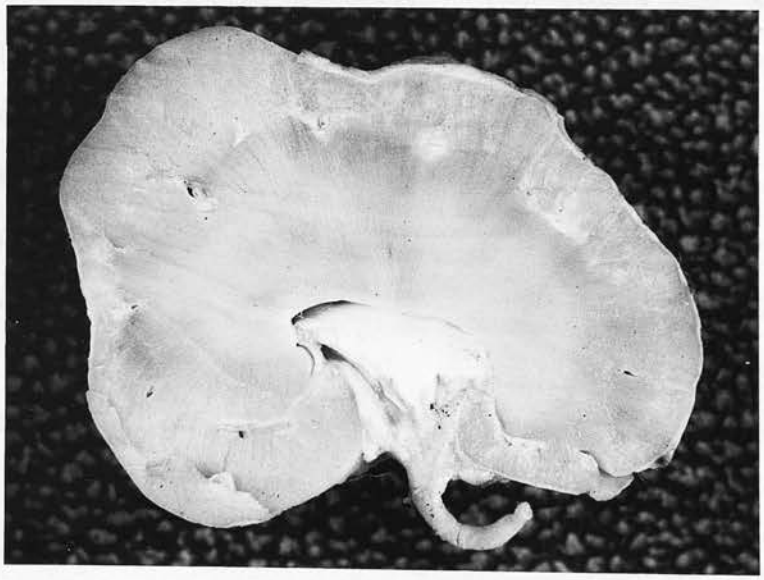

Fig. 20. Secondary renal stage. Irregular narrowing of cortex. Case 471. x $2\frac{1}{2}$.

conformity with the surface granularity (Figs. 20, 21 and 22).

Microscopically, there is diffuse fibrosis throughout the cortex often accentuated in the corticomedullary boundary zone (Figs. 23, 24 and 25) to an extent corresponding to the nodular cellular area observed in the primary stage. Vestigial tubules and isolated capillaries traverse this area. Much of the fibrous tissue in the cortex is perivascular, bands extending alongside small arteries to the capsule where they are inserted. Scattered throughout the cortex are foci of infiltration by mononuclear cells chiefly lymphocytes. These lesions are never as severe as seen in the acute stage and do not contain any polymorphonuclear leucocytes.

The glomerular changes vary greatly in degree but appear to follow a similar pattern commencing with a hyaline thickening of Bowman's capsule. There is also a varying degree of periglomerular fibrosis (Fig. 26). The tufts are sometimes undamaged although a thickening of the basement membrane can usually be demonstrated. Hyaline plaques in the interstices of the tufts can be seen (Figs. 27 and 28). In cases of longer standing complete hyalinisation of the glomerulus takes place (Figs. 29 and 30) with subsequent atrophy of the tubule. Some of the tubules are compressed while other are dilated. The dilatation is particularly well marked in some of the

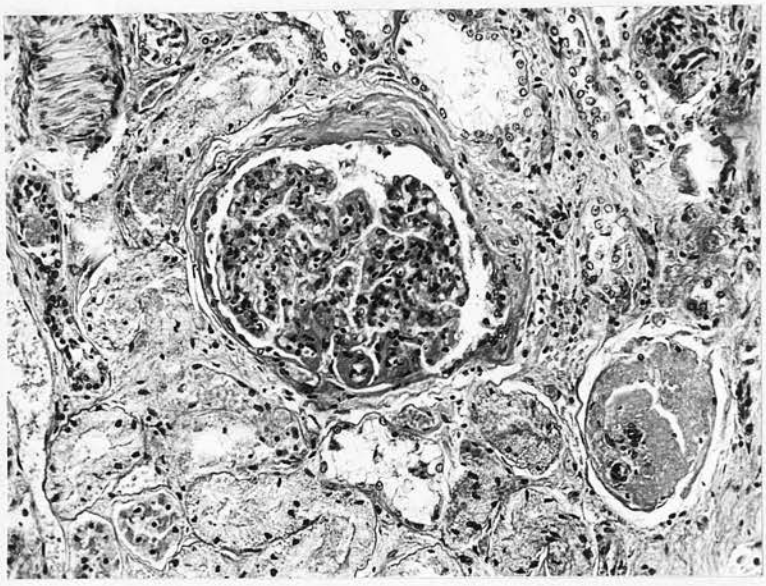

Fig. 29. Secondary renal stage. Periglomerular fibrosis. Hyalinised glomerulus. Case 299. H. and E. x 100.

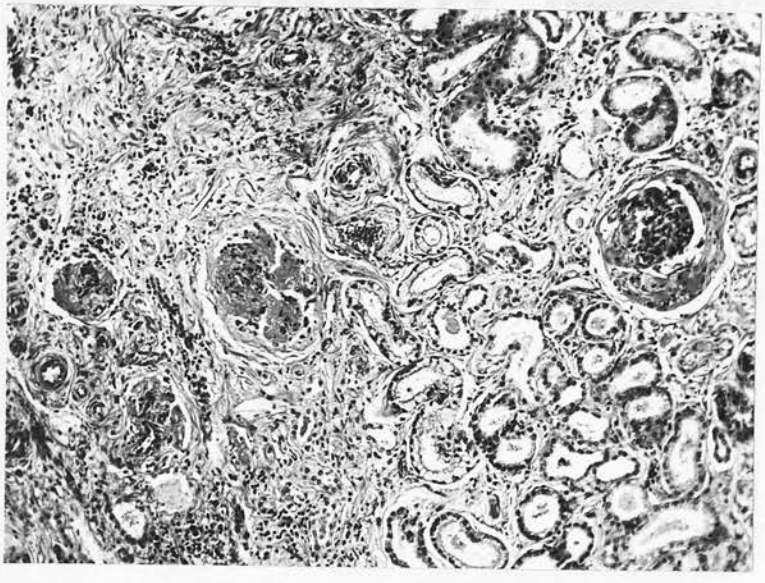

Fig. 30. Secondary renal stage. Hyalinisation of glomeruli. Case 269. H. and E. x 100.

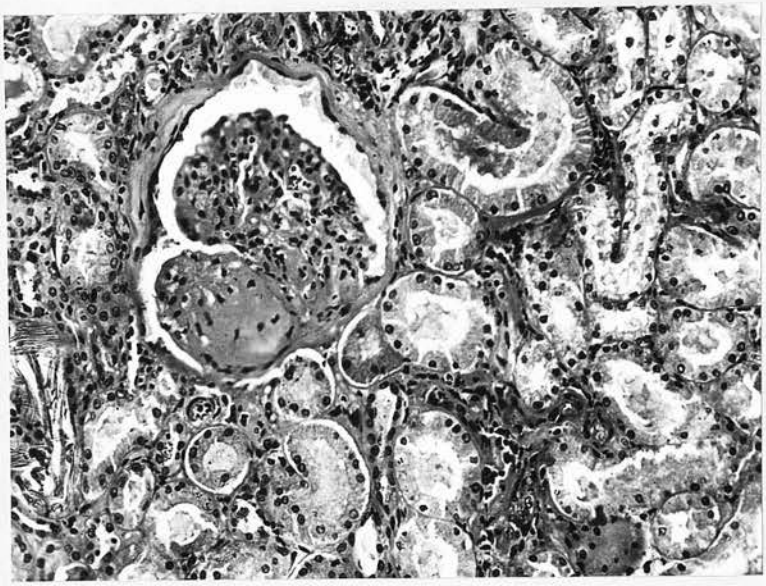

Fig. 27. Secondary renal stage. Hyaline change in glomerulus. Case 293. H. and E. x 100.

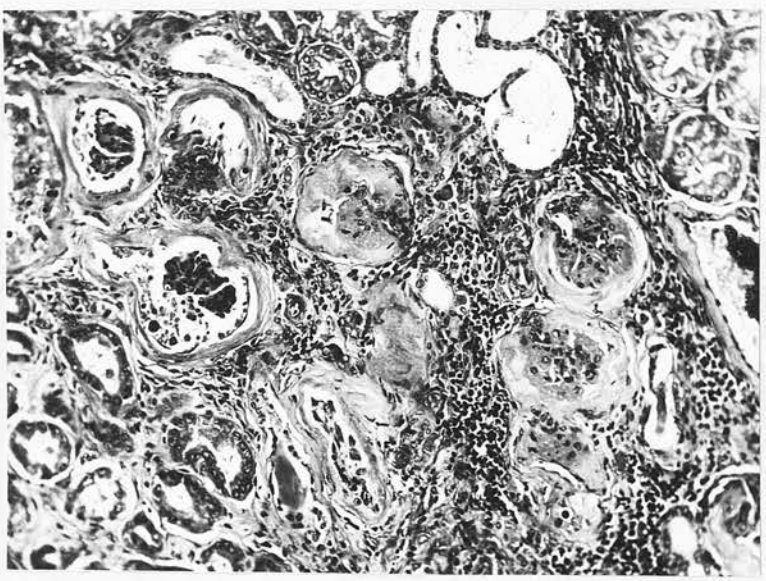

Fig. 28. Secondary renal stage. Fibrosed and hyalinised glomeruli. Case 299. H. and E. x 100.

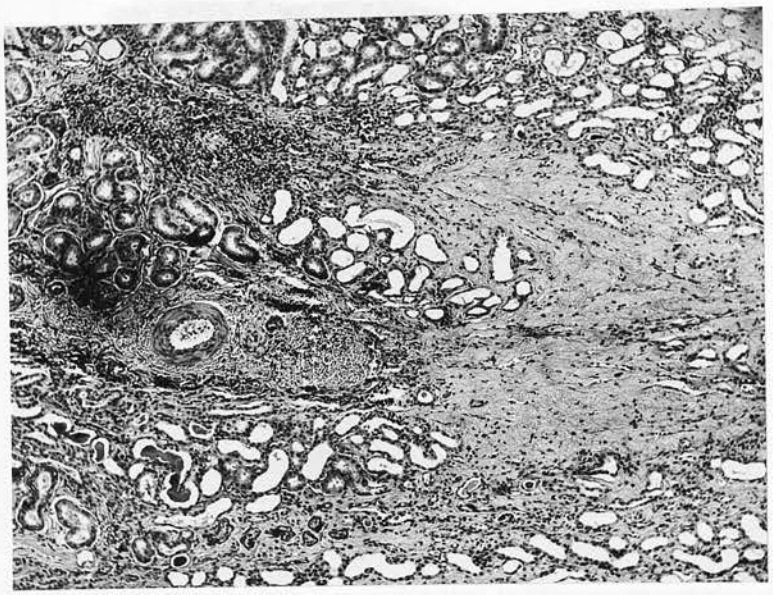

Fig. 25. Secondary renal stage. Boundary zone scars. Case 467. H. and E. x 90.

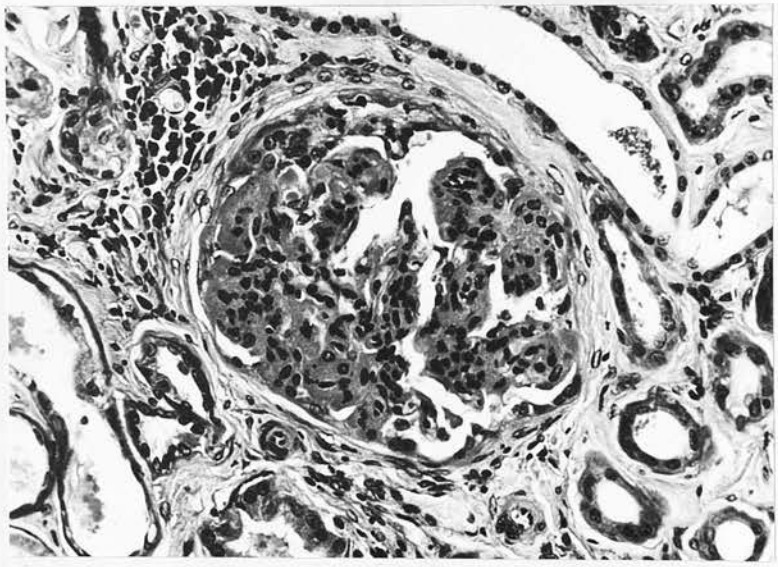

Fig. 26. Secondary renal stage. Periglomerular fibrosis. Case 467. H. and E. x 375.

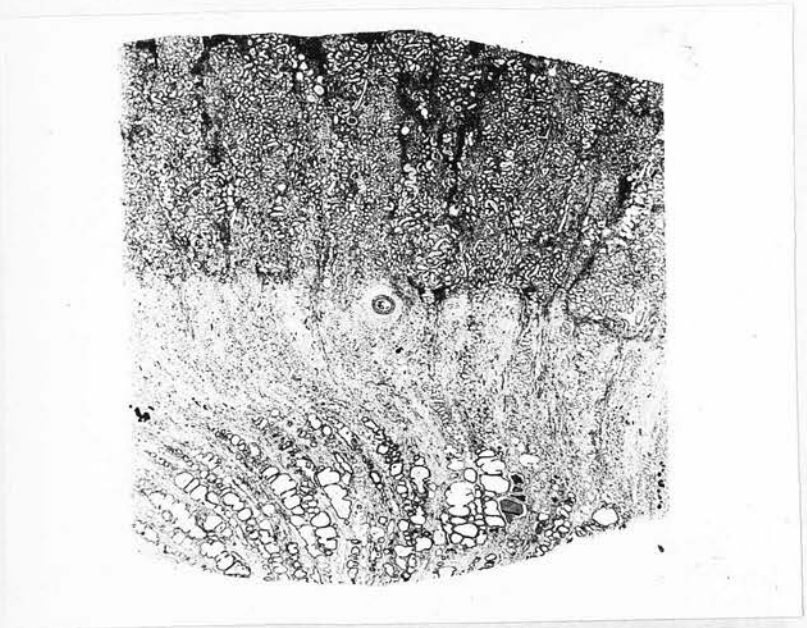

Fig. 23. Secondary renal stage. Boundary zone fibrosis and tubular dilatation. Case 467. H. and E. x 9.5.

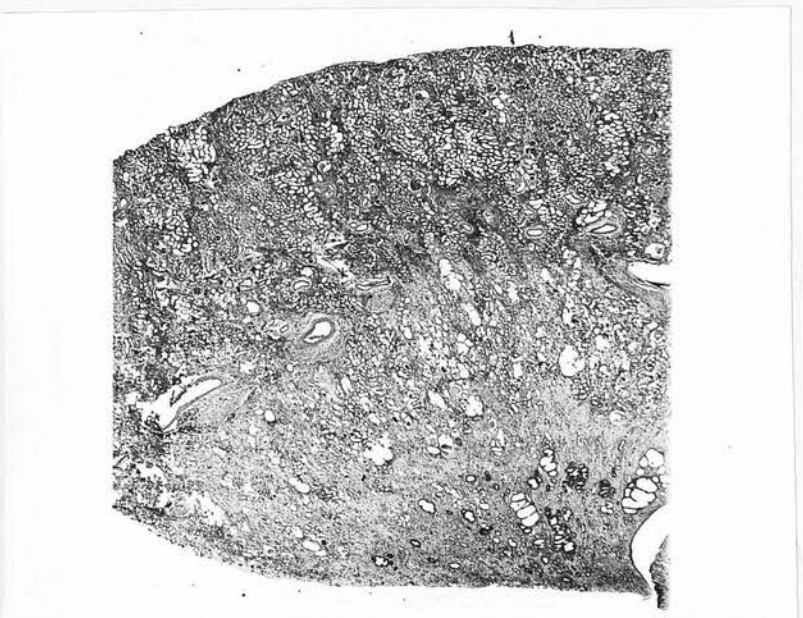

Fig. 24. Secondary renal stage. Boundary zone fibrosis and tubular dilatation. Case 300. H. and E. x 9.5.

Fig. 21. Secondary renal stage. Granular contracted kidney. Case 479. x $2\frac{1}{2}$.

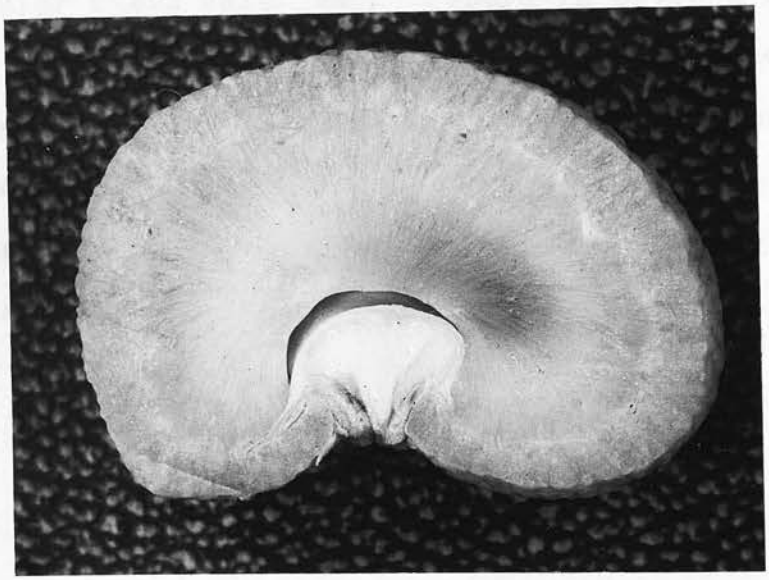

Fig. 22. Secondary renal stage. Narrowing of cortex. Case 479. x $2\frac{1}{2}$.

collecting tubules (Figs. 31 and 32) where several layers of columnar epithelium replace the normal. The tubules so affected are those which are cut off by scar tissue or cellular infiltration. In contrast to this the epithelium of the renal pelvis is normal in appearance. Occasionally there is some slight mononuclear infiltration apparent in the pelvis.

In the interlobular arteries there is muscular hypertrophy (Figs. 28 and 30) with thickening of the internal elastic laminae. The afferent arterioles have muscular walls of increased thickness and some of these show hyaline degeneration. These changes correspond to those observed in the glomeruli and would appear to be the result of hypertension.

Spirochaetes are much more scanty than in primary cases and are found in the tubules (Fig. 33) only after a detailed search of the section. Sometimes they are found embedded in hyaline tubular casts (Fig. 34). There is often a focus of lymphocytes or plasma cells proximal to the tubule containing the spirochaetes. The maximum time which had elapsed in any one case from the time of the primary renal stage to the discovery of spirochaetes in the kidneys at death in the secondary renal stage was $3\frac{1}{2}$ years.

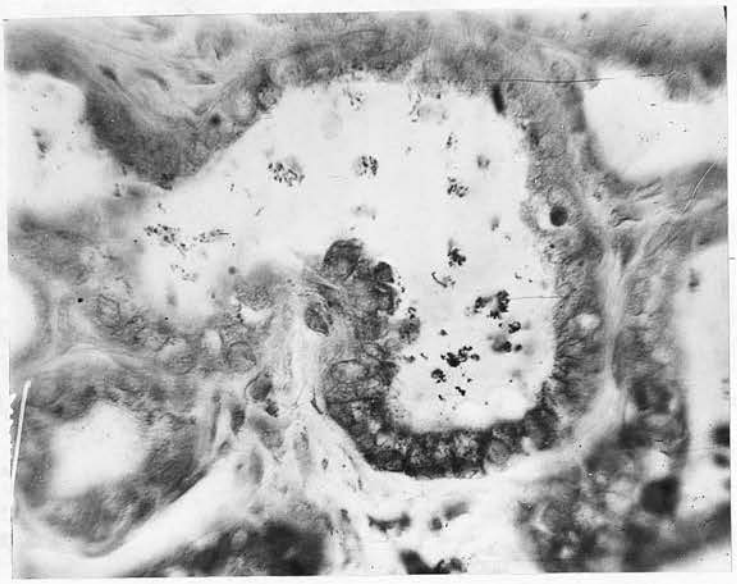

Fig. 33. Secondary renal stage. Leptospirae in convoluted tubule. Case 221. Levaditi. x 480.

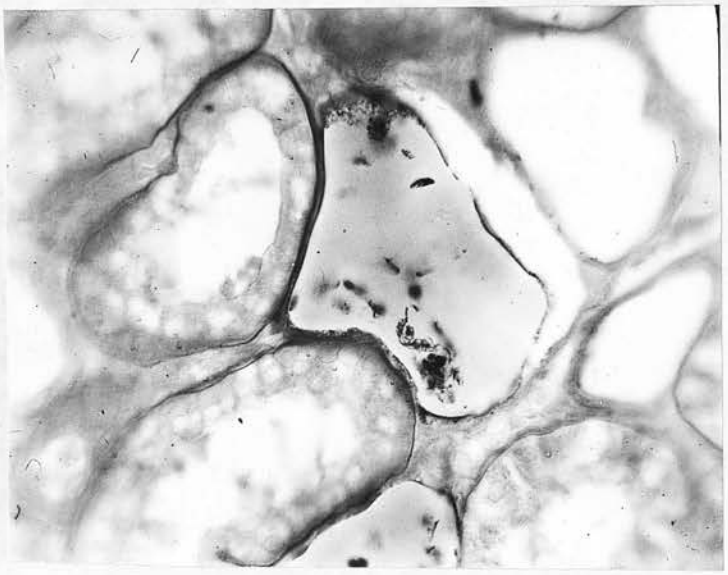

Fig. 34. Secondary renal stage. Leptospirae in albuminous tubular cast. Case 269. Levaditi. x 480.

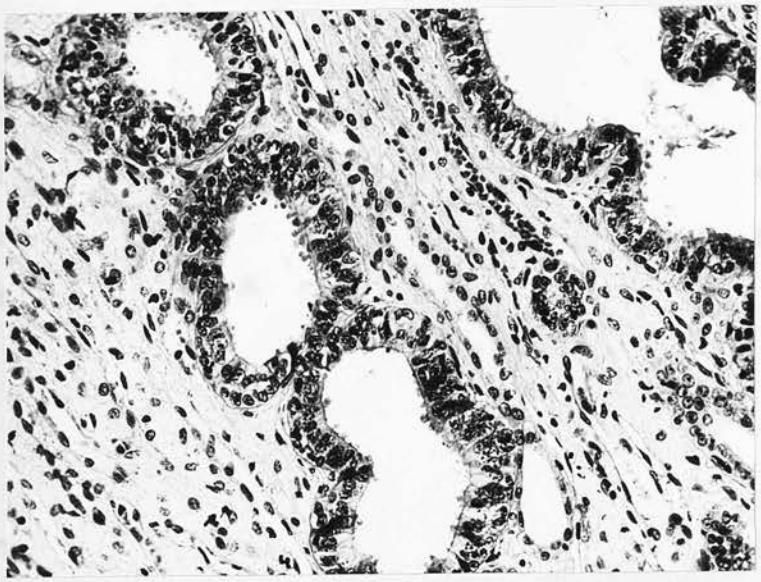

Fig. 31. Secondary renal stage. Tubular dilatation.
Case 467. Duration of illness 4 months. H. and E. x 120.

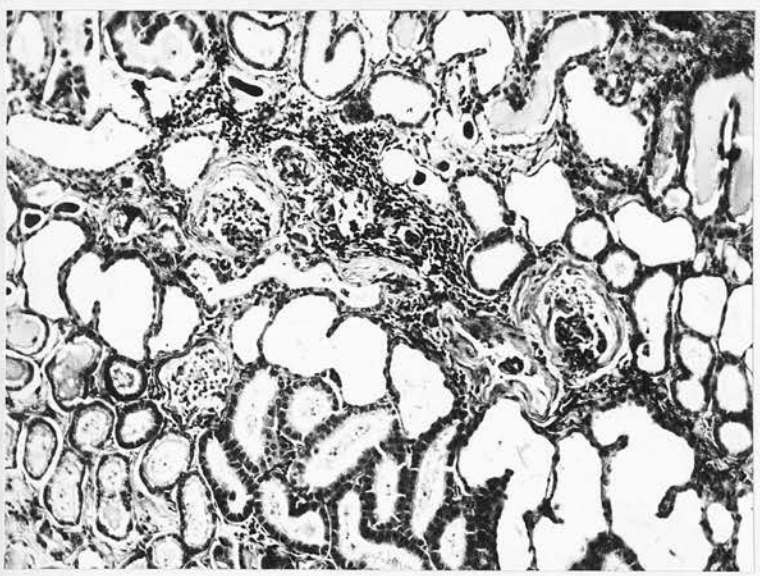

Fig. 32. Secondary renal stage. Tubular dilatation.
Case 221. Duration of illness 14 months. H. and E. x 100.

To show the correlation between clinical, serological, biochemical findings and renal lesions 40 cases have been described in detail below, 20 of them being in the primary renal stage and 20 in the secondary.

Primary Cases

Case 43

Collie, male, 14 months; ill for two months before examined; titre L.C. 1/3,000; no leptospiruria; blood urea 98 mg./100 ml.; destroyed.

Renal pathology

Well marked boundary zone lesion in kidney; diffuse cellular infiltration with fibrosis; scattered cellular nodules in cortex; thickening of Bowman's capsule; cloudy swelling and necrosis of tubule cells; scanty leptospires; transitional subacute case.

Other lesions

Buccal ulceration.

Case 110

Fox Terrier, male nine months; distemper fits and primary leptospirosis; titre L.C. 1/30,000; blood urea 56 mg./100 ml.; died of fits.

Renal pathology

Kidneys apparently normal; only a few very small foci of interstitial cellular infiltration; no glomerular or tubular lesion; no spirochaetes.

Other lesions

None.

Case 143

Cocker Spaniel, male, two years; moribund; titre L.C. 1/30,000; leptospiruria; blood urea 400 mg./100 ml.; leucocytosis; destroyed.

Renal pathology

Marked interstitial cellular infiltration accentuated in boundary zone; considerable fibrosis in boundary zone; focal and diffuse infiltration throughout cortex; some periglomerular fibrosis; much tubular cell degeneration; leptospires in tubules; subacute case.

Other lesions

Buccal ulceration.

Case 150

West Highland Terrier, male, 1½ years; typical severe primary; titre L.C. 1/30,000; blood urea 415 mg./100 ml.; no leptospiruria; leucocytosis; died six days later.

Renal pathology

Kidneys enlarged; diffuse cellular infiltration with scattered intense nodules; some fibrosis in boundary zone; slight thickening of Bowman's capsule; tubular cloudy swelling and necrosis; scanty leptospires in a few tubules.

Other lesions

Lingual ulcers; ulcerative endocarditis.

Case 224

Bull Terrier, male, seven months; moribund; titre L.C. 1/30,000; blood urea 740 mg./100 ml.; leptospiruria; destroyed.

Renal pathology

Grossly enlarged kidneys; marked white band across corticomedullary zone and some white foci in cortex; intense boundary zone cellular infiltration of lymphocytes and plasma cells; some polymorphonuclear leucocytes; obliteration of many glomeruli and tubules; isolated foci in cortex; little change in surviving glomeruli; much tubular cloudy swelling and fatty change; numerous casts in lumina; numerous leptospires in tubules.

Other lesions

Haemorrhagic gastrointestinal mucosae; buccal ulcers.

Case 228

Mongrel Terrier, male, four years; severe primary after 10 days' illness; titre L.C. 1/30,000; blood urea 412 mg./100 ml.; leptospiruria; moribund in four days; destroyed.

Renal pathology

Swollen kidneys with smooth mottled surface; marked grey zone at cortico-medullary junction; massive boundary zone infiltration with widespread tubular destruction; relatively few foci in the cortex; mostly mononuclear cells, also foci of polymorphonuclear leucocytes; slight thickening of basement membrane of glomeruli; extensive cloudy swelling of tubules; numerous spirochaetes in tubules.

Other lesions

Small endocardial lesions.

Case 236

Mongrel Terrier, male, six months; typical severe primary; titre L.C. 1/30,000; blood urea 313 mg./100 ml.; leptospiruria; dead two months later.

Renal pathology

Shrunken kidneys; narrowing of cortex; well marked boundary zone fibrosis with areas of intense interstitial cellular infiltration; some periglomerular fibrosis; widespread tubular cloudy swelling and necrosis; scanty leptospires; subacute

case.

Other lesions

Haemorrhagic gastrointestinal mucosae.

Case 242

Labrador, male, nine months; moribund; titre L.C. 1/10,000; blood urea 450 mg./100 ml.; leptospiruria; destroyed.

Renal pathology

Marked boundary zone cellular infiltration; also diffuse in cortex; mainly lymphocytes with foci of polymorphs; some exudation into Bowman's capsule; much tubular obliteration and necrosis of cells; spirochaetes numerous.

Other lesions

Ulcerative endocarditis.

Case 268

Cairn Terrier, male, two years; typical severe primary; titre L.C. 1/30,000; blood urea 320 mg./100 ml.; leptospiruria; moribund in 12 days despite penicillin therapy; titre L.C. 1/10,000.

Renal pathology

Some kidney contraction; diffuse cellular infiltration with well marked fibrosis in boundary zone; some glomeruli

shrunken; some thickening of Bowman's capsule; much tubular distortion; hyaline cast formation; spirochaetes present; a transitional subacute case.

Other lesions

None.

Case 270

Alsatian, male, seven months; distemper and mild leptospirosis; titre L.C. 1/30,000; leptospiruria; blood urea 53 mg./100 ml.; dead in 18 days with continuous fits.

Renal pathology

No visible renal lesion; only a few scattered inflammatory cells in interstitial tissue; occasional cellular focus; no leptospires.

Other lesions

None.

Case 294

Mongrel Terrier, male, $2\frac{3}{4}$ years; typical severe primary; titre L.C. 1/30,000; blood urea 256 mg./100 ml.; leptospiruria; moribund in nine days despite penicillin therapy; blood urea 588 mg./100 ml.; destroyed.

Renal pathology

Kidney enlarged; areas of intense cellular infiltration

in cortex and boundary zone - mostly plasma cells and lymphocytes with some small foci of polymorphs; Bowman's capsule thickened; cloudy swelling; necrosis and obliteration of tubules; cast formation; numerous spirochaetes in tubules.

Other lesions

Haemorrhagic gastrointestinal mucosae; ulcerative endocarditis.

Case 422

Mongrel Terrier, male, seven months; typical severe primary; titre L.C. 1/30,000; blood urea 289 mg./100 ml.; improved in 10 days - blood urea 49 mg./100 ml.; distemper fits six weeks later; destroyed; titre L.C. 1/1,000; blood urea 40 mg./100 ml.

Renal pathology

Plasma cell and lymphocyte interstitial infiltration; some intense nodules; some early interstitial fibrosis; normal glomeruli; tubular cell cloudy swelling and necrosis; leptospires in tubules.

Other lesions

Endocarditis.

Case 436

Bulldog, female, three years; moribund after several

weeks illness; titre L.C. 1/10,000; blood urea 414 mg./100 ml.; proteinuria but no leptospiruria; destroyed.

Renal pathology

Marked diffuse and focal cellular infiltration of mononuclear cells, lymphocytes and plasma cells; much tubular damage in infiltrated areas; little glomerular change; albuminous exudate into Bowman's capsule; leptospiræ in tubules.

Other lesions

Lingual ulcers; ulcerative endocarditis; haemorrhagic gastrointestinal mucosae.

Case 443

Aberdeen Terrier, male, 18 months; moribund; titre L.C. 1/30,000; blood urea 335 mg./100 ml.; leucocytosis; proteinuria and tubular casts; destroyed.

Renal pathology

Kidneys enlarged; acute diffuse mononuclear cell infiltration in cortex and cortico-medullary zone; foci of polymorphonuclear cells; many tubules obliterated; much cloudy swelling and necrosis; tubular casts; glomeruli relatively undamaged but some exudation into Bowman's capsule; leptospirae numerous in tubules.

Other lesions

Buccal ulcers.

Case 481

Longnosed Collie, male, two years; moribund; titre L.C. 1/30,000; blood urea over 200 mg./100 ml.; destroyed.

Renal pathology

Kidneys enlarged; extensive grey lesions in cortex; intense diffuse cellular infiltration of mononuclear leucocytes and lymphocytes in cortex; much cloudy swelling and necrosis of tubules; glomerular exudation and some thickening of Bowman's capsule; numerous spirochaetes in tubules.

Other lesions

Ulcerative endocarditis.

Case 487

Collie, male, two years; moribund; titre L.C. 1/30,000; blood urea 500 mg./100 ml.; leptospiruria; destroyed.

Renal pathology

Enlarged kidneys; marked grey band in boundary zone; intense cellular infiltration, nodular in appearance; mainly mononuclear with scattered polymorphs; relatively few foci in cortex; exudation into Bowman's capsule; much tubular obliteration; necrosis and cloudy swelling of cells; numerous spirochaetes in tubules.

Other lesions

Buccal ulceration.

Case 488

Cairn Terrier, male, seven months; severe primary; titre L.C. 1/30,000; blood urea 162 mg./100 ml.; no leptospiruria but proteinuria and casts; dead in 10 days despite penicillin therapy; blood urea before death 335 mg./100 ml.

Renal pathology

Extensive grey areas in boundary zone; diffuse and focal cellular infiltration - mostly plasma cells; considerable fibrosis from boundary zone to capsule in strands; thickened basement membrane of glomeruli; obliteration of tubules; increase in arterial muscular coat; lesion becoming subacute; leptospires in tubules.

Other lesions

None.

Case 489

Alsatian, male, five months; moribund; titre L.C. 1/30,000; blood urea 840 mg./100 ml.; no leptospiruria but proteinuria and casts; destroyed.

Renal pathology

Some contraction of kidneys; intense diffuse interstitial cellular infiltration - mostly mononuclear with foci of polymorphs; some early fibrosis; glomeruli relatively unaffected; much tubular cloudy swelling, necrosis and

obliteration; leptospires in tubules.

Other lesions

Buccal ulceration; crumbling endocardial lesions in left atrium.

Case 499

Labrador, female, two to three years; moribund; titre L.C. 1/30,000; blood urea 792 mg./100 ml.; no leptospiruria but proteinuria and casts; leucocytosis; destroyed.

Renal pathology

Kidneys normal size; widespread diffuse interstitial cellular infiltration - mostly plasma cells and lymphocytes; no glomerular change; tubular cloudy swelling and necrosis; leptospires in tubules.

Other lesions

None.

Case 507

Cairn Terrier, male, 19 months; typical severe primary; titre L.C. 1/300,000; blood urea 201 mg./100 ml.; leptospiruria, proteinuria and casts; leucocytosis; dead in four days despite penicillin therapy; blood urea before death 618 mg./100 ml.

Renal pathology

Intense cellular infiltration in boundary zone; also diffuse in cortex; nodular appearance; mononuclear cells predominate; also foci of polymorphs; some thickening of Bowman's capsule; much tubular degeneration; slight early fibrosis; spirochaetes in tubules.

Other lesions

Ulcerative endocarditis; haemorrhagic gastrointestinal mucosae.

Secondary Cases

Case 142

Collie cross, male, 1½ years; moribund from intestinal haemorrhage of unknown origin; titre L.C. 1/1,000; blood urea 58 mg./100 ml.

Renal pathology

Kidneys normal size; small subcapsular depressions; moderate degree of cellular infiltration in cortex; some diffuse fibrosis; periglomerular fibrosis; thickening of Bowman's capsule; some shrunken glomeruli; arteries and arterioles thickened, with fibrosis of wall; hyaline tubular cast formation; scanty spirochaetes in tubules.

Other lesions

Much haemorrhage into wall and lumen of intestine.

Case 145

Mongrel Fox Terrier, male, 11½ years; history of gradual loss of weight; titre L.C. 1/300; blood urea 35.8 mg./100 ml.; destroyed.

Renal pathology

Kidneys normal size and appearance; fair degree of periglomerular fibrosis; some glomeruli markedly shrunken; hyaline change in a few; small areas of cellular infiltration

chiefly plasma cells often near altered glomeruli; some diffuse fibrosis; few spirochaetes.

Other lesions

Hepatic cirrhosis; fibrotic nodules on atrioventricular valves.

Case 147

Mongrel Fox Terrier, male, 14 years; thirst and polyuria for four years; terminal uraemia; titre L.C. 1/30; blood urea 160 mg./100 ml.; anaemia.

Renal pathology

Marked shrunken kidney with granular surface; thin cortex; grossly fibrosed; broad band of fibrosis mostly structureless with a few rudimentary tubules in lower half of cortex and corticomedullary zone; grossly dilated tubules with hypertrophy of wall several layers deep; fibrosis and hyalinisation of many remaining glomeruli; cloudy swelling of some tubules; well marked strands of fibrosis extending to the capsule and ending in one of the subcapsular depressions; some plasma cell and lymphocyte infiltration in these fibrosed areas; scanty leptospires.

Other lesions

Left ventricular hypertrophy; fibrosed nodules on atrioventricular valves.

Case 152

Springer Spaniel, male, 19 months; first examined because of incontinence two to three months after vague illness; titre L.C. 1/10,000; blood urea 90 mg./100 ml.; severe relapse 10 days later; penicillin therapy response; 22 months later typical terminal uraemia; titre L.C. 1/100; blood urea 235 mg./100 ml.; destroyed.

Renal pathology

Small contracted granular kidneys with marked narrowing of cortex; gross fibrosis of cortex extending in linear areas to capsule; marked fibrosis of medulla just subcortical; in fibrosed areas glomeruli appear completely fibrosed and some hyalinised; well marked areas of infiltration with lymphocytes and plasma cells; arterial muscular coats thickened; cloudy swelling in proximal tubules near cellular infiltration; scanty leptospirae in tubules.

Other lesions

Nodules on atrioventricular valves.

Case 162

Cocker Spaniel, male, two years; moribund; titre L.C. 1/100; blood urea 420 mg./100 ml.; anaemia; destroyed.

Renal pathology

Small contracted kidneys; marked boundary zone fibrosis

with slight diffuse cellular infiltration; periglomerular fibrosis and hyalinisation of glomeruli; tubular epithelium hyperplasia; scanty spirochaetes.

Other lesions

Nodules on atrioventricular valves.

Case 166

Greyhound, male, one year; repeated distemper fits; titre L.C. 1/1,000; blood urea 35.3 mg./100 ml.; destroyed.

Renal pathology

Kidneys apparently normal; slight diffuse cellular infiltration with occasional small areas of fibrosis; slight thickening of Bowman's capsule; some tubular cloudy swelling; spirochaetes scanty; probable subacute case.

Other lesions

None.

Case 177

Collie, male, 11 years; moribund in terminal uraemia; titre L.C. 1/100; blood urea 291 mg./100 ml.; anaemia; destroyed.

Renal pathology

Small granular contracted kidneys with narrow cortex; advanced fibrosis particularly at boundary zone with some

diffuse cellular infiltration; glomeruli shrunken and hyalinised; periglomerular fibrosis; cloudy swelling of convoluted tubules; many collecting tubules cystic in appearance; hyperplasia of epithelium; no spirochaetes.

Other lesions

Left ventricular hypertrophy.

Case 190

Fox Terrier, male, eight years; moribund after gradual loss of weight over three months; bad teeth; titre L.C. 1/100; blood urea 190 mg./100 ml.; destroyed.

Renal pathology

Small contracted granular kidneys with narrow cortex; much interstitial fibrosis with some diffuse cellular infiltration; glomeruli show fibrosis of capsule; some completely hyalinised; tubular dilatation; arterial muscular coat thickened; no leptospires.

Other lesions

Buccal ulceration.

Case 192

Aberdeen Terrier, male, 12 years; thin and moribund; titre L.C. 1/300; blood urea 193 mg./100 ml.; destroyed.

Renal pathology

Small contracted kidneys; marked boundary zone fibrosis with diffuse fibrosis of cortex; some foci of lymphocytes; marked periglomerular fibrosis and shrinking; tubular dilatation and hyaline casts; scanty leptospirae in tubules.

Other lesions

Well marked valvular nodules; left ventricular hypertrophy.

Case 220

Collie, male, four years; typical secondary with nitrogen retention; thirst and polyuria for one year; titre L.C. 1/300; blood urea 286 mg./100 ml.; no leptospiruria; moribund 10 days later; destroyed.

Renal pathology

Very small contracted granular kidneys; thin cortex; little functioning renal tissue; widespread fibrosis particularly dense at boundary zone; some diffuse cellular infiltration; most glomeruli show some fibrosis and hyalinisation; cloudy swelling of remaining tubules; marked hyperplasia of epithelial wall of collecting system; leptospires in tubules.

Other lesions

Haemorrhagic gastrointestinal wall.

Case 221

Mongrel Terrier, male, six months; typical severe primary with titre L.C. 1/30,000; blood urea 136 mg./100 ml.; leptospiruria and proteinuria; recovered with penicillin therapy; 14 months later terminal uraemia with titre L.C. 1/3,000; blood urea 592 mg./100 ml.; no leptospiruria; destroyed.

Renal pathology

Small granular kidneys with narrow cortex; marked diffuse fibrosis; foci of intense infiltration of lymphocytes and plasma cells just subcapsular; marked degree of periglomerular fibrosis; many glomeruli completely fibrosed and hyalinised; tubular dilatation most marked in subcortical medulla; arterial thickening and fibrosis well marked; considerable cast formation, mostly hyaline; leptospirae in tubules.

Other lesions

Buccal ulcers; haemorrhagic gastrointestinal mucosae; left ventricular hypertrophy.

Case 246

Collie, male, $2\frac{1}{2}$ years; moribund in typical terminal uraemia; titre L.C. 1/100; blood urea 322 mg./100 ml.; no leptospiruria.

Renal pathology

Small kidneys with very thin cortex; gross distortion of

renal structure; only slight cellular infiltration; glomeruli with periglomerular fibrosis and some completely fibrosed; dilatation and proliferation of epithelium of collecting tubules; all arteries and arterioles greatly thickened; leptospiruria in tubules.

Other lesions

Buccal ulcers.

Case 269

Cocker Spaniel, male, one year; typical secondary in terminal uraemia with fits; titre L.C. 1/1,000; blood urea 369 mg./100 ml.; destroyed.

Renal pathology

Kidneys slightly shrunken; subcapsular depressions on surface; advanced fibrosis with considerable interstitial cellular infiltration, mostly plasma cells; some glomerular fibrosis; tubular cloudy swelling; no spirochaetes.

Other lesions

Buccal ulcers.

Cases 279, 299 and 300

Three Bull Terriers, male, two years; litter of six; acute febrile illness when six months; two months later mother dead of acute nephritis; fourth animal (case 301) alive at $5\frac{1}{2}$

years - titre L.C. 1/300, no nitrogen retention, proteinuria and tubular casts on six examinations over 3½ years; fifth dead at three years of suspected renal failure; sixth dead in motor accident.

Case 279

Typical secondary with uraemia; titre L.C. 1/100; blood urea 200 mg./100 ml.; no leptospiruria; moribund 10 days later with blood urea 584 mg./100 ml.; aged two years.

Renal pathology

Granular contracted kidneys with adherent capsule; narrow cortex; advanced interstitial fibrosis; marked fibrosis and hyalinisation of many glomeruli; cloudy swelling of tubules and cast formation; considerable interstitial cellular infiltration, mostly lymphocytic; fibrosis of arteries and arterioles; leptospirae in tubules.

Other lesions

Buccal ulceration.

Case 299

Well at two years; titre L.C. 1/3,000; blood urea 58.8 mg./100 ml.; no leptospiruria; nine months later typical secondary with nitrogen retention; kept alive for two months with persistent uraemia; destroyed at two years 11 months - blood urea 193 mg./100 ml., titre L.C. 1/300, no leptospiruria

but proteinuria and tubular casts.

Renal pathology

Contracted granular kidneys; fibrosis more advanced than 279 and only sparse cellular infiltration; extraordinary degree of hyalinisation of glomeruli; widespread proliferation of tubular epithelium with dilatation; marked hypertrophy of arterial muscular coat; leptospirae in tubules.

Other lesions

Left ventricular hypertrophy; small nodules on atrioventricular valves.

Case 300

Well at two years; titre L.C. 1/300; blood urea 66.4 mg./100 ml.; no leptospiruria; nine months later typical terminal uraemia; titre L.C. 1/30; blood urea 540 mg./100 ml.; proteinuria but no leptospiruria; destroyed.

Renal pathology

Contracted kidneys with pitted surface; advanced diffuse fibrosis; some foci of cellular infiltration; marked periglomerular fibrosis; cloudy swelling of many convoluted tubules; arterial wall thickening; leptospirae in tubules.

Other lesions

Left ventricular hypertrophy.

Case 284

Golden Labrador, male, 1½ years; moribund; titre L.C. 1/1,000; blood urea 465 mg./100 ml.; no leptospiruria.

Renal pathology

Contracted granular kidneys; extensive diffuse fibrosis; small foci and some perivascular bands of cellular infiltration; glomeruli shrunken and fibrosed; dilated, cystic tubules in cortex and medulla; epithelial hyperplasia in collecting tubules; thickening and fibrosis of arteries and arterioles; cast formation; no leptospires.

Other lesions

Some nodules on atrioventricular valves.

Case 291

Mongrel Fox Terrier; secondary case; titre L.C. 1/1,000; blood urea 155 mg./100 ml.; destroyed.

Renal pathology

Some kidney contraction; diffuse fibrosis with some well marked areas completely fibrosed in juxtamedullary zone; residual mononuclear cell infiltration; glomerular fibrosis; tubular cloudy swelling; marked arterial thickening; leptospirae in tubules.

Other lesions

Left ventricular hypertrophy.

Case 293

Bull Terrier, male, five years; moribund; titre L.C. 1/300; blood urea 265 mg./100 ml.; died.

Renal pathology

Kidneys contracted with irregular thinning of cortex; diffuse interstitial fibrosis with well marked areas in boundary zone; also some well marked cellular foci; glomeruli fibrosed; some tubules dilated with marked proliferation of epithelium; arterial thickening; no leptospirae in tubules.

Other lesions

None.

Case 296

Collie, male, four years; moribund; terminal uraemia with fits; titre L.C. 1/100; blood urea 580 mg./100 ml.; no leptospiruria.

Renal pathology

Markedly shrunken kidneys with narrow cortex; extraordinary boundary zone fibrosis; only slight focal cellular infiltration; diffuse fibrosis of cortex; fibrosed and hyalinised glomeruli; marked tubular dilation and hyperplasia of epithelial wall; thickening and fibrosis of all arteries; some leptospires in tubules and some in hyaline casts.

Other lesions

None.

Discussion on Sections 1 and 2

The information gained from the examination of 369 dogs which had become infected with L. canicola indicates that the primary infection usually occurs early in life. This is probably explained by the fact that in an urban community dogs are exposed to infectious diseases at an early age. That there appears to be no age immunity is borne out by the fact that two dogs were seven years old and six dogs five years old before becoming infected.

In the present series there were nine males affected for every female. In the dog population passing through the clinic it was found that the ratio was three males to one female. After allowing for this population ratio infection with L. canicola would appear to be three times as common in the male as in the female. This is probably due to the greater tendency of the male to lick or sniff at freshly voided urine or the vulva and preputial orifice of passing dogs.

It is impossible to assess accurately the significance, if any, of the preponderance of certain breeds in the series but it possibly reflects the popularity of the various breeds in the area. The mongrel terrier, the collie and the mongrel collie are the types which are most readily available from pet

shops. Cocker Spaniels and Alsatians are popular as household pets and watchdogs respectively.

Although a bacteraemia capable of producing pyrexia and anorexia has been demonstrated in seven cases, the majority of dogs infected with L. canicola did not show signs of a bacteraemic stage of sufficient severity to induce their owners to seek veterinary advice. On the other hand the owners of some dogs which were not examined until the primary renal stage gave a history of a mild malaise having occurred some seven to 10 days previously. The presence of a bacteraemia has also been demonstrated experimentally in pups (vide infra) the optimum time for recovering the organism being the third or fourth day after infection. It is interesting to note that in two naturally occurring cases the organism was recovered from bloods in which there was a high level of circulating agglutinins and that in one of these two cases leptospirae were observed in the urine. In experimentally infected dogs agglutinins were not found in the blood simultaneously with organisms but attempts at recovery were not made later than the fifth day after infection (vide infra).

There does not appear to be any other report of the demonstration of a bacteraemia in naturally occurring or experimentally produced infections with L. canicola in dogs.

The term primary renal stage was chosen to describe a group of cases which varied greatly in the severity of symptoms shown, the degree of nitrogen retention and in the extent of the renal lesion. The symptoms encountered varied from thirst and polyuria in an otherwise apparently normal dog to the severe depression, emesis and ensuing coma of advanced uraemia. The renal lesion varied from sparse cortical foci to a massive cellular infiltration at the cortico-medullary junction or an intense diffuse infiltration throughout the cortex.

As it was difficult if not impossible to decide whether many of the mild cases were in the primary or secondary stage on clinical examination only a combination of serological and bacteriological data was used to differentiate these cases. Any animal with agglutinins at a dilution of 1/10,000 or higher was taken to be in the primary stage. If it were found that on two successive examinations at an interval of a week or more the titre rose from 1/1,000 to 1/3,000, the dogs showing this rise were classified as primary cases. A few cases showing leptospiruria and a titre of 1/3,000 were also called primary.

The adoption of this more detailed classification eliminates a great deal of the confusion which arises from attempts

to diagnose cases from the owner's history and physical examination only. Pathological examination has supported this classification except in so far as a small number of cases had developed renal fibrosis in addition to a cellular infiltration before the titre had fallen below 1/10,000. These cases could be described as subacute and could be separated clearly from the more advanced cases of secondary change (vide infra). They give some indication of the rapidity with which renal fibrosis can develop in the dog as it was found from the follow up of naturally occurring and experimental cases that the agglutination titre climbed rapidly to a maximum within two weeks and then fell gradually below 1/10,000 by the end of the sixth or eighth week. This suggests that renal fibrosis has developed in two to three months when found in dogs having high titres but experimental proof is still required.

The incidence of readily detectable leptospiruria (50-70%) provides a relatively simple method of diagnosis in at least half of the naturally occurring primary cases. It should be noted that only uncentrifuged urine was examined by dark field microscopy in this series. It is possible that an even higher percentage of cases of leptospiruria could have been detected by centrifugation of the urine and dark ground examination of the deposit. It is interesting to note

the correlation between the level of agglutination titre and the incidence of leptospiruria. The higher the titre the more common was leptospiruria. This is probably explained by the time that the titre takes to rise and fall. Low titres represent cases which are either in the early stages, before leptospiruria has had time to develop, or in the later stages when leptospiruria has been eliminated by treatment or natural recovery. Although leptospiruria was not readily detectable by dark ground examination of the urine in those cases leptospirae were found often in large numbers in the kidneys at autopsy. These were demonstrated by Levaditi's method and were most easily seen in the lumen of the tubules which indicated that they would eventually enter the bladder urine. These spirochaetes were found even in cases which had received a course of penicillin therapy before death. It is possible that any difficulty in finding leptospirae in the bladder urine is due to the presence of agglutinins and to the greatly lowered pH of the urine in some of the more severely affected cases. The duration of leptospiruria was not studied as the dogs had to be treated with antibiotics in the interests of the health of the animal and of the owner.

Routine examination of the urine of affected cases for protein and tubular casts has shown that a proteinuria is

readily detectable in all cases examined and that when a thorough search is made there are usually present a few tubular casts. One of the most striking features is that the numbers of casts in urines examined seldom showed any correlation with the severity of the animal's condition as evidenced by physical appearance and the degree of nitrogen retention. In some there was a massive number of tubular casts but many of the severe cases showed only a few. This finding was borne out by histological examination of the kidneys. While casts were apparent in the majority of sections examined they were never numerous save in a small number of advanced chronic cases.

The study of dogs for as long as four years after the primary infection has shown the remarkable persistence of proteinuria with the excretion of tubular casts of agglutinating antibodies and of leptospirae in the kidneys. In no single instance of 46 dogs examined for periods varying from six months to four years after the initial infection did agglutinins or proteinuria disappear. Leptospirae have been demonstrated in the kidney tubules at post mortem examination as long as $2\frac{1}{2}$ years after penicillin therapy had been administered in the primary renal stage.

The renal lesion produced by L. canicola is primarily an

acute interstitial cellular infiltration of varying intensity. This lesion had been demonstrated at autopsy in naturally occurring cases and in cases produced by experimental infection (vide infra). The infiltration has a marked compressive action on tubules and causes obliteration when extensive. Its most striking feature in the severe cases is the intense zone of reaction produced at the cortico-medullary junction. Why this degree of localisation should be produced is problematical but it is possible that it is the result of the operation of a renal shunt during a severe bacteraemic phase. Trueta et al. (1947) have shown that a shunt of arterial blood can take place through the glomeruli situated in the cortico-medullary zone producing a temporary cortical ischaemia. Various stimuli were used by these workers such as trauma and pituitrin and it may be that a bacteraemia with pyrexia and toxaemia such as occurs in leptospirosis will produce a similar shunt and allow a greater preponderance of organisms to settle out in that area. There is little doubt that this pattern tends to dominate the distribution of the renal lesion in the severe cases. Although it is not so evident in the histological pattern of milder acute cases it is well marked in many chronic cases which have survived the acute phase. In these cases a solid band of almost structureless fibrous tissue has replaced the

cellular infiltration. The contraction resulting causes much interference with the remaining blood supply to the cortex and with the nephrons and collecting system of tubules. It may be that this juxta-medullary zone of fibrous tissue plays the dominant part in precipitating renal failure when it occurs at an early age in chronic cases.

Apart from the fibrosis another striking change in these chronic kidneys is the intense proliferation of the epithelium of the collecting tubules. Many are dilated to several times the usual diameter and are lined by two or even three layers of tall hyperplastic cells. Why this change should primarily affect the collecting system which has suffered the least damage must await further explanation.

While spirochaetes were demonstrated readily in the lumen of tubules in acute cases it was never possible to identify them in the zones of cellular infiltration although argentiphilic granules were often present. Krivacek and Lukes stated that they had found spirochaetes in 17 of 21 dogs and in 97 of 105 dogs, respectively, usually in convoluted tubules near the glomeruli. They found only a few in the interstitial tissue but Krivacek regarded the many black "coccal" forms as altered forms of spirochaetes. Jelinek (1925) and Klarenbeek (1927) made a similar hypothesis. If these

granules in the cellular exudate were accepted as degenerated leptospirae it would offer a reasonable explanation of the intense cellular reaction. That the infection is haematogenous in origin has been demonstrated by the recovery of the organism from the blood during the bacteraemic stage. As no organisms or any significant cellular reaction was found in the glomeruli it appears that the leptospirae pass through the glomerular capillaries and gain their predilection site in the interstitium via the efferent arterioles. Here they set up a cellular reaction and some of them probably penetrate the walls of the tubules and so enter the urine. In the lumina of the tubules they can be more easily detected and are often found in clumps. Alternatively they may gain their interstitial locus via the glomerular filtrate and penetrate the tubular wall in the opposite direction.

It is difficult to offer an explanation for the persistence of spirochaetes in the tubules for several years after penicillin therapy. Neimand (1940) states that leptospiruria may continue for 18 months and Wirth (1937) has described it as continuing for seven months after experimental inoculation. In several of the cases in this series which were eventually autopsied as long as three years after receiving penicillin therapy it was still possible to

demonstrate spirochaetes. These were found in the lumina of convoluted tubules placed in the superficial zone of the cortex. Invariably proximal to these infected tubules there was a focus of plasma cells and mononuclear cells. These spirochaetes may exist in the lumen of the tubules where they are often situated in structureless hyaline casts or they may have penetrated the tubular wall from the surrounding interstitium. Further work requires to be done to demonstrate the infectivity of these organisms. In the meantime it must be presumed that these are viable and a potential source of infection for other animals. How these organisms came to be protected from the penicillin therapy in the first place or from antibody is difficult to understand unless it be that the anatomical structure of the interstitium makes this possible. It is doubtful if the continuing foci of spirochaetes play a significant part in the production of renal failure in the secondary stage. The total damage done to neighbouring tubules is probably relatively small.

The arterial changes in the kidneys are indicative of a gradually mounting hypertension. The thickening of the muscular coat and the deposit of fibrous tissue and the advanced hyalinisation of the glomeruli in some cases were the most striking features. These changes were always accompanied by

left ventricular hypertrophy. Clinically, most of the secondary cases are described as having a hard pulse which means an increase in the force of the pulse wave accompanied by a loss of elasticity of the arterial wall. Increased blood pressures were recorded in 16 cases in the secondary renal stage.

It is difficult to assess the part that these arterial changes play in the development of renal failure. Experiments are in progress to measure more accurately the significance of the hypertension produced. It is probable that in those chronic cases in which there is a considerable degree of proteinuria (3-7 gm. per 24 hour volume of urine) and in which the hyalinisation of glomeruli is extensive the vascular lesion plays a significant if not dominant role in producing renal failure.

Section 3.

Experimental infection of dogs with Leptospira canicola.

Introduction

Once the disease syndrome associated with Leptospira canicola had been studied and described as it occurred in the dog in this country it became necessary to see if the organism isolated from a case of naturally occurring infection would set up a similar disease in dogs infected experimentally. This is obligatory to fulfil Koch's postulates which demand also the isolation of the organism from the experimental animal.

Apart from the gaining of this basic knowledge there were a number of other points of special interest which required elucidation. In the above discussion the hypothesis has been made that dogs probably infect themselves by smelling or licking the vulva and preputial orifice or freshly voided urine. This inferred that the organism could gain entrance to the body via the nasal and/or buccal mucous membranes and that infection could pass from dog to dog. These questions could only be decided by experimental work.

Wirth (1937) had already demonstrated that leptospiruria could persist for as long as seven months when he used a

spirochaete isolated from a case of Stuttgart disease. It was probably L. canicola although it was not typed antigenically. It was therefore decided not to study the duration of leptospiruria in the meantime, but only to establish its occurrence.

Monlux (1948) described a leucocytosis and an increased erythrocyte sedimentation rate in experimental infection in the dog using a strain of leptospira not typed antigenically. Because of these interesting observations and because of the earlier finding of a leucocytosis in the naturally occurring primary renal cases it was decided to follow the blood changes in some of the experiments conducted.

Once it was established that an infection with L. canicola could be set up in the puppy by different routes of administration of the organism the main preoccupation of my work became the production of severe renal lesions. From observations on naturally occurring cases it was known that chronic renal fibrosis and histological changes characteristic of hypertension could develop in a period of months from the date of the initial infection provided that the initial lesion had been severe enough. If this succession of events could be produced in experimental animals it would have an interest far greater than the study of the lesions produced by L.

canicola. For it would provide a method of producing experimental hypertension in dogs by the action of a tissue response to an infective process and extend the knowledge at present gained from hypertension experiments using clamps on the renal artery. Several experiments have been carried out using different methods of setting up an infection in an attempt to produce really severe primary lesions. The experiments are described below and the results discussed later.

Materials and Methods

Pups were bought from a pet shop between three and four months old. Collies or Mongrel Terriers were used for all the experiments. As females were cheaper to procure than males they predominate numerically in this series of experiments. They were kept as a separate group isolated from other animals.

The Broom strain of L. canicola, originally isolated from a dog by J. C. Broom, The Wellcome Foundation, was used throughout the series of experiments. Subcultures grown in Schuffner's medium were used when four, five or six days old.

Details of dose and route of administration are given with each experiment.

Experiment 1

One male Collie pup, five months old, No. 320G, was given 5 ml. Leptospira canicola culture intraperitoneally. The blood and urine changes were studied. Apart from not eating its food on the fourth day and having a temperature of 103.5° F. this puppy appeared normal throughout the course of the experiment. The pup was destroyed on the 23rd day after inoculation. Details of examinations are given in Tables 10 and 11.

Table 10

Days after Inoc.	Blood Culture	Agglutination titre L. C.	Agglutination titre L. I.	Blood Urea mg/100 ml	Lepto-spiruria	Protein-uria mg/100ml	Tubular Casts
-1	-	-	-	29	-	-	-
1	-	-	-	30			
2	-	-	-	33			
3	-	-	-	35			
5	+	-	-	32			
6	-	300	30	40	-	20	+
7	-	1,000	300	35			
8	-	3,000	300	42	-	5	+
9	-	10,000	1,000	26			
12		10,000	1,000	28			
13		10,000	1,000	35	+	5	+
15		30,000	1,000	45	-	Trace	-
19		10,000	300	30	-	Trace	+
23		10,000	300	41			

Table 11

Days after Inoc.	BSR mm./ hour	PCV %	Hb. gm./ 100ml.	RBC 10^3/ c. mm.	Total WBC/ c. mm.	NLN	LN	Bas.	Eos.	Lym.	Mon.
-1	0	35	12	4,600	11,600	4	42	1	0	52	1
1	0	40	12	4,300	16,100	3	38	3	0	47	2
2	1	36	11.4	4,400	16,000	5	54	0	1	35	3
3	2	35	12.3	4,500	12,200	3	66	0	0	30	1
5	20	36	12.3	4,500	13,700	2	48	1	0	25	4
6	10	35	11.5	4,600	17,200	3	75	1	0	17	4
7	4	37	11.7	4,300	6,800	1	58	0	0	36	5
8	4	35	11.7	5,000	8,000	3	60	0	0	31	6
9	2	33	11	4,300	7,700	3	54	2	1	35	5
12	8	29	10.2	4,000	10.800	2	46	2	1	44	5
13	0	33	11.2	4,200	14,600	2	62	2	2	28	2
15	10	34	11.5	4,600	23,400	4	76	0	0	16	1
23	3	43	12.2	4,800	12,600	6	82	0	0	13	4

NLN = Non-lobulated Neutrophil.

LN = Lobulated Neutrophil.

Post mortem examination

Kidneys normal in size; scattered focal lesions throughout cortex; well marked interstitial cellular infiltration of lymphocytes and plasma cells; occasional polymorphonuclear leucocyte; glomeruli normal; some cloudy swelling of tubular

cells; no vascular lesion; spirochaetes scanty in tubules.

No other lesions were found. Spirochaetes were demonstrated by dark ground microscopy of an emulsion of kidney and Leptospira canicola was isolated in pure culture from this emulsion.

Discussion

Repeated blood and urine examinations were carried out on this dog because it was the first to be infected in the series of experiments being described.

It was found that a culture of L. canicola, originally isolated from another dog, was capable of infecting pup No. 320G and causing a mild malaise during the bacteraemic stage, an increased erythrocyte sedimentation rate, a moderate leucocytosis, and a renal lesion similar to those observed in naturally occurring cases. As the blood urea figures show the renal lesion was not sufficiently severe to cause nitrogen retention. The pattern of the rise and fall of circulating agglutinins is also demonstrated by the repeated agglutination tests.

L. canicola was recovered in pure culture from the blood five days after infection. Proteinuria and tubular casts were demonstrated on the sixth day and leptospiruria on the thirteenth day. At autopsy spirochaetes were demonstrated

in a kidney emulsion. Finally a subculture of the isolated organism was used to infect another dog described in the next experiment thus fulfilling the requirements of Koch's postulates.

Experiment 2

5 ml. subculture of the strain of L. canicola which had been isolated from case 320G 12 days before was inoculated intraperitoneally into two female puppies, three months old, Nos. 359G and 361G. 359G did not eat its food on the fourth day after inoculation but did not have a rise in temperature. Pup 361G had had severe diarrhoea a few days previously but had recovered. A week after the inoculation it became suddenly very ill and died. Autopsy revealed numerous hepatic abscesses. No histological examination of this pup was carried out. Details of examinations carried out on these two pups are given in Tables 12 and 13.

Table 12

Days after Inoc.	Blood Culture	Agglutination titre L. C.	Agglutination titre L. I.	Blood Urea mg/100ml	Lepto-spiruria	Protein-uria mg/100ml	Tubular Casts
Case 359G							
2	Contam-inated	-	-	18			
3	+	-	-	24			
4		-	-				
8					-	20	+
15		10,000	1,000	40	+	10	+
26		30,000	100				
38		1,000	30		-	5	+
40		1,000	30				
47		1,000	100	32	-	5	+
Case 361G							
2	Contam-inated	-	-	20			
3		-	-	31			
4	+	-	-				
8	Died suddenly.						

Table 13

Days after Inoc.	BSR mm./ hour	PCV %	Hb. gm./ 100ml.	RBC 10^3/ c. mm.	Total WBC/ c. mm.	NLN	LN	Bas.	Eos.	Lym.	Mon.
Case 359G											
2	0	38	10.2	5,300	10,500	9	88	0	0	1	2
3	45	34	12	5,000	16,200	6	89	0	0	3	1
4	8	32	-	+	18,200	6	87	0	0	4	0
45	0	42	13	5,600	11,900	3	68	0	1	27	1
Case 361G											
2	3	30	9.5	4,600	11,600	2	76	0	0	21	1
3	8	33	9.94	4,800	13,600	1	67	0	0	29	1
4	2	30	-	-	10,000	7	83	0	0	7	1

NLN = Non-lobulated Neutrophils.

LN = Lobulated Neutrophils.

Post mortem examination of case No. 359G

Kidney normal in size; well marked white areas on cut surface; marked infiltration especially at boundary zone; mostly lymphocytes and plasma cells; glomeruli relatively normal; widespread tubular cloudy swelling and necrosis; leptospirae numerous in tubules.

No other lesions.

Discussion

It is probable that the death of Case 361G was not connected with the leptospiral infection. It is interesting to note the much smaller increase in E.S.R. in this case compared with a considerable rise in 359G. The leucocyte response is also less in 361G.

The renal lesions recorded in these cases (Figs. 35, 37, 38) are among the most extensive produced in this series of experiments but even these were not sufficient to produce nitrogen retention. The lesions could be seen readily by naked eye examination of the cut surface of the cortex as well marked grey areas. Microscopically they resemble in every way the interstitial cellular infiltration which is typical of naturally occurring cases. Leptospires were readily demonstrated (Fig. 36) in the convoluted tubules. It is possible that this well marked renal lesion represents some increase in virulence of the organism as a result of its passage through case 320G.

Experiment 3

One adult, male, Collie of two years old, case 353G, was inoculated intraperitoneally with 5 ml. of a subculture of the strain of L. canicola isolated from case 359G 23 days earlier.

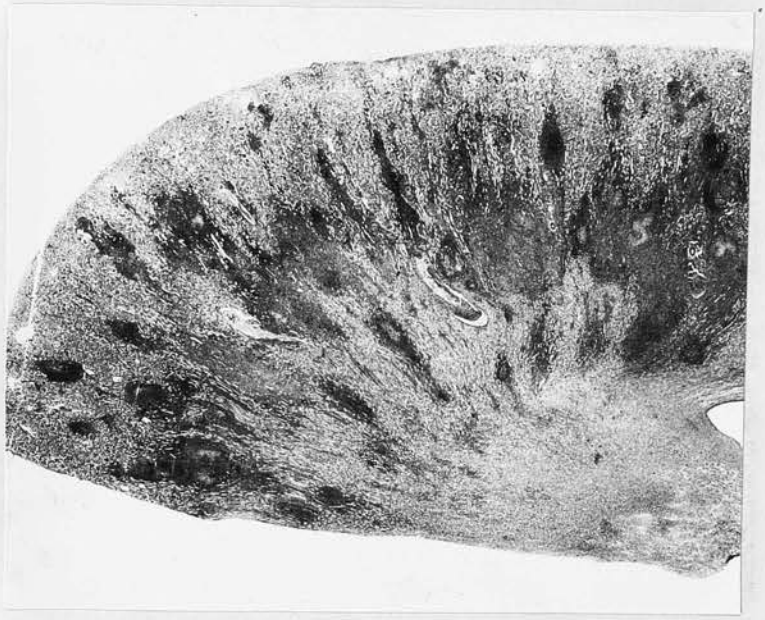

Fig. 35. Experimental infection. Case 359G.
Cortical and boundary zone infiltration. H. and E. x 8.

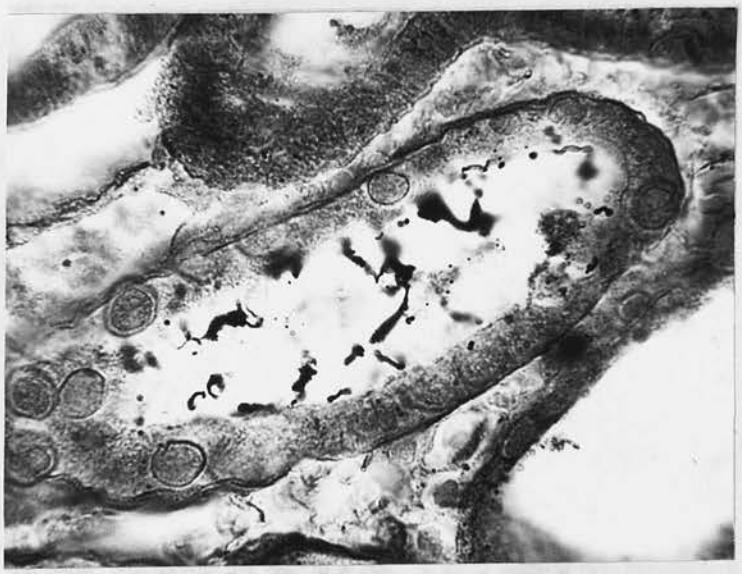

Fig. 36. Experimental infection. Case 359G.
Spirochaetes in tubule. Levaditi. x 1100.

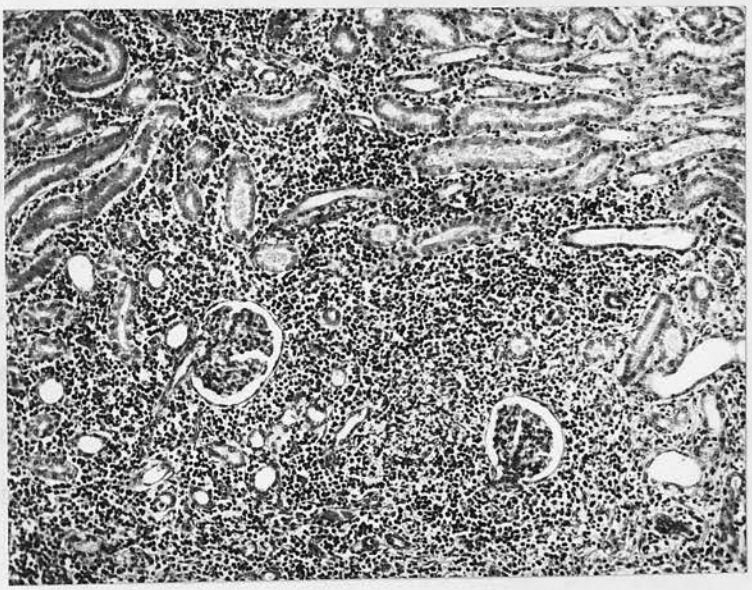

Fig. 37. Experimental infection. Cellular infiltration. Case 359. H. and E. x 110.

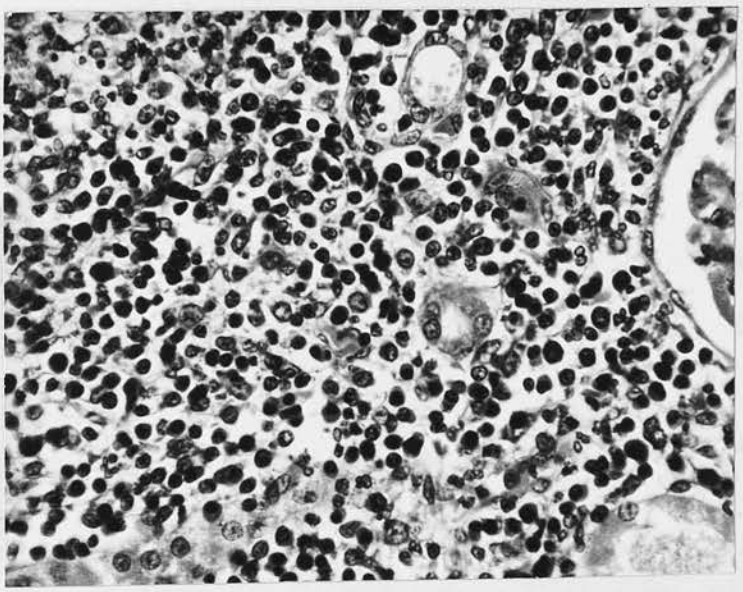

Fig. 38. Experimental infection. Cellular infiltration. Case 359. H. and E. x 410.

The dog was known to have a titre of 1/100 against L. icterohaemorrhagiae and to be passing a small amount of protein in the urine along with a few casts before the experiment began. Leptospira canicola was isolated from the blood in pure culture on the fourth day after inoculation. Subsequent urine examinations continued to yield proteinuria and tubular casts. Details of successive agglutination tests are given below.

Table 14

Days after Inoculation.	Agglutination Titre L. C.	L. I.
Case 353G		
-2	-	100
4	-	30
13	3,000	300
20	3,000	300

The dog was destroyed at the twentieth day after inoculation. Small, focal, but well marked lesions were found in the kidneys. The cellular infiltration was lymphocytic with some plasma cells present. No evidence of fibrosis from a past infection was present. Leptospirae were demonstrated in the convoluted tubules. (Fig. 40)

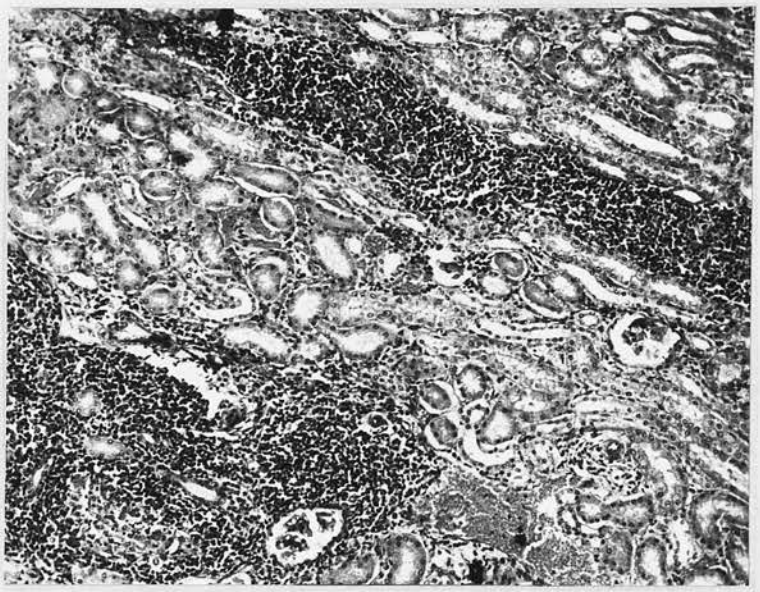

Fig. 39. Experimental infection. Intense local cellular infiltration. Case 1298. H. and E. x 110.

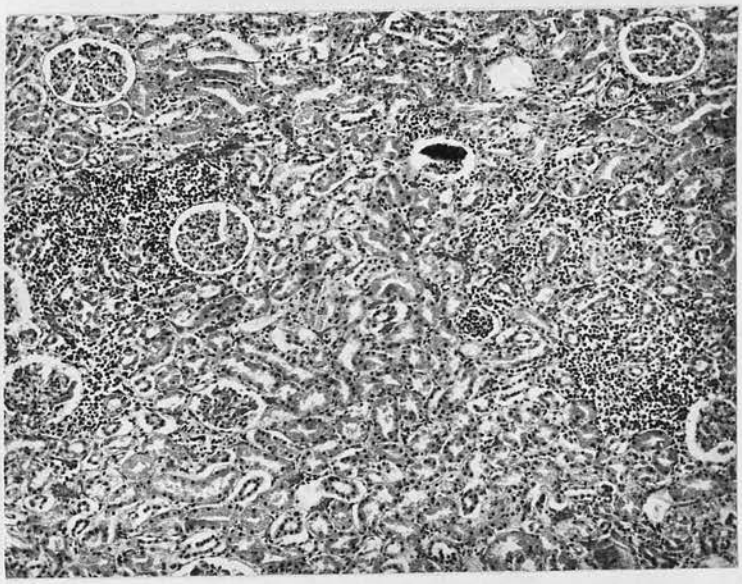

Fig. 40. Experimental infection. Mild diffuse cellular infiltration. Case 353. H. and E. x 110.

Discussion

From the serological and urinary evidence it would appear that this dog had previously suffered from a very mild leptospiral infection probably icterohaemorrhagiae in type. The renal lesion must have been small and localised as it was not recognisable histologically in the section examined. It is interesting to note that it was possible to establish an infection with L. canicola despite the presence of these agglutinins although they may have produced some protective effect by lessening the severity of the lesion. Although the organism used in this case had recently been passaged through two other dogs its virulence does not seem to have been greatly enhanced. It may be that because it was subcultured in vitro three times before being used again it had lost virulence once more.

Experiment 4

One female Collie pup, three months old, case No. 362G, was placed in the same cage as case 359G 26 days after the latter had been infected with a second passage strain of L. canicola. Leptospiruria had been demonstrated in case 359G on the fifteenth day after infection.

No malaise was detected in case 362G and it was destroyed 64 days after exposure to infection from case 359G. The two cases had shared the same cage for 21 days before 359G was destroyed. Details of the development of agglutinins are given in Table 15.

Case 362G — Table 15

Days after Inoculation	Agglutination Titre L. C.	L. I.	Blood Urea mg./100 ml.
-1	-	-	28
7	-	-	30
13	10	-	33
28	3,000	300	33
50	3,000	300	44

Post mortem examination

Normal kidney in appearance; microscopically, numerous but small scattered focal lesions; mostly lymphocytes with a few plasma cells; some tubular cloudy swelling; only a few spirochaetes in Levaditi sections.

No other lesions.

Discussion

The point of interest in this experiment lies in the fact that pup 362G contracted an infection with Leptospira canicola

during the three weeks, (probably during the first two weeks according to the agglutination titre) in which it shared a cage with pup 359G in which leptospiruria had been demonstrated. Once again there was no nitrogen retention and the lesions were small despite the fact that this was a dog to dog infection and that case 359G had exhibited lesions a good deal more severe. This indicates that other factors may influence the severity of infection produced, such as length of time during which the carrier dog has been shedding leptospires. It is probable that the nearer an infection is to the peak of its antibody response the greater the exposure the organism receives to antibodies in the urine. Whether the organism gained entry to pup 362G via the buccal or nasal mucosa or through the skin remains unknown. That the mucous membrane can be penetrated readily by L. canicola is illustrated in the next experiment.

Experiment 5

One male Terrier pup, five months old, case 478G, was infected with a subculture of L. canicola by instilling 2 ml. into each nostril and holding the head in a tilted position for a minute. Two days later the dog was anorexic and dull but not pyrexic. The anorexia lasted only two days. On the

fourth day after infection the organism was isolated from the blood in pure culture. Proteinuria was detected on the fourth day after infection and leptospiruria on the thirteenth. Details of the development of agglutinins are given along with blood urea levels in Table 16.

Table 16

Days after Inoculation	Agglutination Titre L. C.	L. I.	Blood Urea mg./100 ml.
Case 478G			
-1	-	-	25
4	-	-	26
13	1,000	100	30
21	1,000	100	30

- = negative

Post mortem examination

The kidneys appeared normal; microscopically numerous small but well marked interstitial cellular foci - mostly lymphocytes and plasma cells; little glomerular or tubular change; leptospirae in tubules.

No other lesions.

Discussion

The successful establishment of an infection with L.

canicola by the intranasal route strengthens the hypothesis, although not proving it, that this or the oral is the route of natural infection in street dogs.

Again the infection was a mild one and the antigen response was weak and this is probably due once more to the lack of virulence of the organism.

Experiment 6

Two Mongrel Terrier pups, four months old, one female, the other male, case Nos. 434G and 446G, were inoculated with 10 ml. L. canicola subculture intravenously. They were both apathetic the following day but not anorexic. Both showed elevated temperatures. In three days they were normal again. Details of temperature, blood culture, agglutination titres are given in Table 17. On the 26th day 446G was destroyed as the development of agglutinins had been so poor. Only tiny focal lesions were found in the kidneys. Case 434G was then reinfected by the intraperitoneal route. 7 ml. of subculture was used. On this occasion agglutinins developed to a high level as shown in Table 18 but renal lesions were even smaller than in 446G.

Table 18

Day after Inoculation	Blood Culture	Agglutination Titre L. C.	Agglutination Titre L. I.	Blood Urea mg./100 ml.	Temperature °F
Case 446G					
-1		-	-	36	102.2
1	+	-	-	25	104.4
13		100	-	32	102
19		300	-	41	103
26	Destroyed				
Case 434G					
-1		-	-	40	102
1	+	-	-	42	103
3	+	-	-	32	105
11		100	10	26	102
19		100	30		102
27	2nd inoculation - 7 ml. culture intraperitoneally				
53		30,000	1,000	44	
70	Destroyed	10,000	300	40	

Post mortem examination

446G

Kidneys normal in appearance; few but well established focal lesions - mostly plasma cell infiltration; much cloudy swelling and necrosis of tubular epithelium; no glomerular

lesion; spirochaetes scanty.

No other lesions.

434G

Kidneys normal in appearance; tiny scattered foci of interstitial cellular infiltration in the cortex; no glomerular or tubular damage; no spirochaetes observed.

Discussion

In this experiment the infection has been established by the intravenous injection of the culture. It is interesting that the level of agglutinating antibodies should remain so low when there was a good temperature response to infection in both cases. It may be that introduction of the organism directly into the blood gives the defence mechanism the maximum opportunity of destroying the organism quickly.

The first inoculation in case 434G did not produce a strong enough immunity to resist the intraperitoneal inoculation of a second dose. Agglutinating antibodies developed rapidly to a high level after the second inoculation.

Once more the lesions in both cases were typical of the disease but very small in extent.

Experiment 7

Three female Collie pups, Nos. 1296, 1297 and 1298, were given 10 ml. of hyperimmune antiserum (Burroughs Wellcome Hard Pad Serum) subcutaneously to protect them from a possible infection with distemper. Later it was observed that this batch of antiserum contained agglutinating antibodies against Leptospira canicola at a titre of 1/300. Four days later they were inoculated with a culture of L. canicola and then given a second inoculation seven days after the initial. Details are given below in Table 19.

Table 19

Pup No.	Agglutination test before inoc.	Dose of initial inoc.	Dose of 2nd inoc. on 7th day	Agglutination test at 6 weeks	Lesions at P.M. after 6 weeks.
1296	L.C. -ve L.I. -ve	5 ml.	5 ml.	L.C. 1:1000 L.I. 1:30	Marked boundary zone.
1297	L.C. -ve L.I. -ve	5 ml.	5 ml.	L.C. 1:1000 L.I. 1:100	Numerous - focal.
1298	L.C. -ve L.I. -ve	5 ml.	5 ml.	L.C. 1:300 L.I. 1:1-	Sparse - focal.

Detailed descriptions of the renal lesions produced in these three pups are given below.

Case 1296

Slightly enlarged kidney; intense diffuse interstitial cellular infiltration accentuated at boundary zone; nodular in appearance; mostly lymphocytes and plasma cells with a few scattered polymorphs; some exudation into Bowman's capsule; widespread cloudy swelling, necrosis and obliteration of tubules; leptospires in tubules.

Case 1297

Kidneys normal in size; numerous scattered focal lesions - lymphocytes and plasma cells; some glomerular exudation; cloudy swelling and necrosis of tubular cells; leptospires in tubules.

Case 1298

Kidneys normal in size; small area of marked cellular infiltration forming a narrow band from medulla to capsule; (Fig. 39) some distinct nodules; entirely mononuclear - lymphocytes and plasma cells; no glomerular change; cloudy swelling; necrosis and localised obliteration of tubules; leptospires mostly in superficial cortex.

Discussion

These three cases gave the most consistent renal lesions of all the experiments carried out. It is unlikely that the second inoculation at an interval of one week was the explanation

as this technique failed to produce similar results when repeated in experiment 9 (vide infra). It may be that this particular subculture was more virulent than others or it may be that the homologous antiserum given four days before the initial leptospiral inoculation produced some unknown effect.

Whatever the reason, it must be remembered that although these lesions were marked they were not as severe as those occurring in some naturally infected cases and they did not produce any obvious malaise in the pups.

Experiment 8

Six Collie pups, four months old, two males and four females, were given an infecting dose of L. canicola culture intraperitoneally followed by a dose of hyperimmune rabbit serum subcutaneously. This serum was capable of agglutinating live cultures at a titre of 1/30,000. Nos. 2535, 2538 and 2539 each were given 5 ml. L. canicola culture intraperitoneally followed by 5 ml. L. canicola hyperimmune serum subcutaneously six days later. Nos. 2536, 2537 and 2540 each were given 5 ml. L. canicola culture intraperitoneally followed by 5 ml. L. canicola hyperimmune serum subcutaneously one day later. Details of agglutinin development and blood ureas are

given in Table 20.

Table 20

Days after Inoculation		Agglutination Titre L. C.	Agglutination Titre L. I.	Blood Urea mg./100 ml.
Case 2535				
-1		-	-	27
3		-	-	
8		300	10	31
24		3,000	30	
62		3,000	-	29
84	Destroyed			
Case 2538				
-1		-	-	40
1		-	-	
8		3,000	300	38
24		30,000	100	46
62		300	-	29
71		100	-	
84	Destroyed			
Case 2539				
-1		-	-	36
3		-	-	
8		3,000	1,000	44
24		3,000	300	44
62		300	-	
71		300	-	
84	Destroyed			
Case 2536				
-1		-	-	42
8		30	-	27
80		30,000	100	
84	Destroyed			

Days after Inoculation	Agglutination Titre L. C.	L. I.	Blood Urea mg./100 ml.
Case 2537			
-1	-	-	40
1	-	-	
8	-	30	32
24	1,000	10	37
62	30,000	100	29
71	30,000	100	
84	Destroyed		
Case 2540			
-1	-	-	47
3	-	-	
8	-	-	26
23	3,000	100	22
62	300	30	27
64	1,000	100	
71	300	30	
84	Destroyed		

- = Negative

Post mortem examination

In all six pups there were no lesions in the kidneys visible to the naked eye. In cases 2535, 2536 and 2537 there were no lesions detectable microscopically in the sections examined, while in the other three cases only a few small foci of cellular infiltration were detectable.

Discussion

If the hyperimmune serum has had any effect on the results at all it would appear to have given some protection to the pups and not increased the severity of the lesion as

had been hoped. In the general discussion on Section 3 these results are compared to those gained by the German workers, Gädeke and Schoenherr, working with hamsters.

Experiment 9

Three female Collie pups, four months old, Nos. 1587, 1588 and 1590, were each given L. canicola culture intraperitoneally. Only 5 ml. was given to No. 1587 and 10 ml. to each of the other two. A week later each was given a second dose intraperitoneally of 3 ml. culture. None of the animals showed malaise. They were destroyed after 30 days at which time they all had an agglutination titre of 1/3,000 against L. canicola. They had not received any prophylactic against distemper.

No. 1587 was the only case in which renal lesions were observed. In this case there were numerous, small foci of interstitial cellular infiltration and some diffuse infiltration also - chiefly lymphocytic. No glomerular lesion was observed but there was some tubular cell cloudy swelling and necrosis. Spirochaetes were detected in the tubules by Levaditi's method.

Discussion

The variation in the results of this experiment are difficult to explain. The only variable factor in method was the fact that case 1587 which showed the best lesions was given 5 ml. as an initial dose while the other two cases received double that dose without producing a recognisable lesion. It hardly seems likely that this dosage factor is the important one. It is probable that the variation was purely an individual one and the lack of good lesions was again due to attenuated virulence of the organism.

Experiment 10

Three female Collie pups, aged five months, Nos. 1443, 1480 and 1481, were not given any prophylactic against distemper. They were inoculated twice with 5 ml. L. canicola culture at an interval of five days. They were destroyed after six weeks.

Case 1480

Agglutination titre before death - L.C. 1/10,000
L.I. 1/10

Blood urea before death - 35 mg./100 ml.

Post mortem

Kidneys normal in appearance; a few small scattered foci of lymphocytes in the cortex; no spirochaetes visible.

No other lesions.

Case 1443

Agglutination titre at death - L. C. 1/300
L. I. negative

Blood Urea - 30 mg./100 ml.

Post mortem

Normal kidneys; only a few small foci of interstitial cellular infiltration observed; no spirochaetes.

No other lesions.

Discussion

The marked difference in the extent of the lesion in one pup, 1480, from the others indicates an individual difference in reaction to the same dose of culture taken from the same container on both occasions. There was no question of any interference by a homologous serum or by antibodies against L. canicola which such a serum might contain as these pups, like those in experiment 9, were given no prophylactic against distemper. The lesions in No. 1480 are well marked but not nearly severe enough to produce renal failure. Giving the

second injection on the fifth day instead of the seventh as in experiment 9 did not increase the severity of the lesion. It was of interest to note that on this occasion the higher the level of agglutinins the more severe was the lesion but as only three pups were used it is probably of little significance.

General Discussion on Section 3

In the above experiments it has been shown that it is possible to set up an infection in the dog with a strain of Leptospira canicola isolated from a naturally occurring case and to recover that organism again in pure culture from the blood of the infected dog and from the kidneys at post mortem examination. The recovered organism was passaged through two further dogs after an intermediate culture and subculture in vitro. In each case pathological lesions in the kidneys similar to those in naturally occurring cases were found at autopsy.

While the majority of infections have been set up by the intraperitoneal route two have been established by the intravenous route and one via the nasal passages. Another puppy was infected by being placed in the same cage as a pup infected 26 days earlier and left in contact for 21 days. All cases infected developed agglutinating antibodies although in some renal lesions were not detectable. No difficulty was thus experienced in infecting 22 puppies and one adult dog by the intraperitoneal, intravenous and intranasal routes. The success of the intranasal route was of particular interest as this has been hypothesised in the discussion on Sections 1 and 2 as being the probable route of natural infection.

Bacteraemia was established in cases infected by all three routes. This adds support to the view that a bacteraemia occurs in naturally occurring cases although not necessarily producing a noticeable malaise.

Leptospiruria was established in three cases along with proteinuria and tubular casts. After this had been done no further attempt was made to examine urines because of the difficulties of securing them from small female puppies.

None of the different methods employed has produced consistently severe lesions in the kidneys. Indeed in five of 23 animals used in these experiments it was impossible to demonstrate any lesion. Nonetheless good lesions have been reproduced, lesions which are identical in character to those found in naturally occurring primary cases. It is probable that if these cases had been allowed to live for longer than the usual one to three months that healing would have taken place by the development of interstitial fibrosis. Spirochaetes were demonstrated by Levaditi's impregnation method without difficulty in the cases in which lesions were well established.

There are several possibilities to account for the difficulty in reproducing severe renal lesions. The first and most obvious one is that the organism became so attenuated when

grown in vitro that it was no longer capable of producing a severe disease. An attempt was made to overcome this difficulty by passaging the organism three times without producing the desired result. It may be that the fact of culturing the organism in between passage was sufficient to attenuate its virulence. An attempt is now to be made to passage the infection from animal to animal by transferring blood taken during the bacteraemic stage to another susceptible animal in a further attempt to increase the virulence of the organism.

In experiments 7, 9 and 10 two successive inoculations were given by the intraperitoneal route with a view to studying the effect produced by a second injection given during a period (fifth to seventh days after the initial injection) when it was presumed the animal had been sensitised but had not yet established an immunity against the disease. This proceedure also did not produce really severe lesions although in one experiment cases 1296, 1297 and 1298 all had well established lesions. It had been thought possible that the most severe naturally occurring cases might have been caused by picking up a second infection during the early primary stage, but the failure in these experiments to produce lesions of a similar severity by using a second inoculation makes this idea improbable.

Whether or not the fact that the pups in experiment 7 received a homologous serum containing agglutinating antibodies against L. canicola had any effect in producing the lesions is difficult to estimate but seems unlikely as it would be expected that the antibodies would tend only to protect against and not enhance the severity of the infection. Severe as these lesions were they did not produce malaise in the pups.

Gädeke and Schoenherr (1951) described the effect of giving hyperimmune L. canicola serum to hamsters 24 hours after inoculation with live culture. Instead of dying in the usual way from a bacteraemia in four to five days these hamsters showed little or no malaise but when killed 12 weeks later had well marked renal lesions. Experiment 8 was carried out to see what would happen if the techniques described by these two workers were used on dogs. Again the results were disappointing in that no severe lesions were produced. Indeed it is probable that the hyperimmune serum had merely a protective action in both the hamster and the dog.

While it has not, so far, been possible consistently to produce severe renal lesions, predominantly in the boundary zone, it has been shown that an infection with L. canicola could readily be set up by several different routes and that

recognisable renal lesions similar to those in the naturally occurring cases could be set up. Koch's postulates have been satisfied and in addition agglutinating antibodies against the infecting organism have been demonstrated in all cases infected.

It can therefore be concluded that Leptospira canicola is capable of setting up an acute interstitial nephritis in experimental pups similar to that demonstrated in naturally occurring cases of the disease but that the factor or factors involved in producing really severe acute lesions with subsequent nitrogen retention remain to be elucidated.

Conclusion

In conclusion it may be stated that a naturally occurring infection with Leptospira canicola in the dog produces an acute interstitial nephritis of varying severity with a marked tendency to localise in the juxta-medullary zone. If the animal survives the acute cellular infiltration the obliterated nephrons are replaced by fibrous tissue, the extent of which, by its tubular and vascular distortion, probably plays a dominant part in the production of renal failure in the secondary or chronic stage. Small numbers of spirochaetes may persist in the kidneys in scattered foci for as long as $2\frac{1}{2}$ years and possibly longer following penicillin therapy but probably do not cause extensive damage. Arterial and glomerular changes, cardiac hypertrophy and a rise in blood pressure indicate the presence of hypertension which may in some cases be the main cause of renal failure in the secondary stage. Agglutinins against L. canicola persist in the blood and protein and tubular casts continue to be excreted in the urine for as long as four years after the initial infection.

Infection has been produced experimentally in dogs by infecting them with a subculture of a strain of Leptospira canicola originally isolated from a dog. The organism has been recovered from the blood and kidneys of experimentally

infected dogs and again transmitted to susceptible dogs thus fulfilling Koch's postulates. Renal lesions, similar in pattern to those observed in dogs which died in the naturally occurring primary stage, have been demonstrated but they were not sufficiently extensive to cause renal failure. It has been suggested that this is probably due to the lack of virulence of the organism.

Summary

369 dogs infected with Leptospira canicola have been examined clinically. Agglutination tests and blood urea estimations have been carried out on each case. Details of examinations are given in the appendices. The cases have been classified into two main groups, primary and secondary renal, according to the agglutination titres and these two groups have been subdivided according to the degree of nitrogen retention as evidenced by blood urea levels. Seven primary cases were shown to have a leptospiral bacteraemia in the early stage. 46 of the primary cases were kept under observation for periods of six months to four years, during which time agglutinins against L. canicola persisted as did proteinuria and the excretion of tubular casts.

In Section 2 the renal lesions associated with L. canicola infection are described. The primary renal stage was characterised by an intense interstitial cellular infiltration which often localised predominantly in the corticomedullary zone. In subacute stages early fibrosis was evident but the infiltration remained the chief feature. In well established cases of chronic nephritis in the secondary stage the main lesion was extensive diffuse fibrosis with comparatively few small cellular foci remaining. Spirochaetes were sparse but

were demonstrated mostly within the lumen of tubules or in the substance of a hyaline cast.

In the experimental work described in Section 3 Koch's postulates have been fulfilled by reproducing the infection in dogs and recovering the organism in pure culture from the blood and kidneys of the infected animal. The recovered organism was then passaged through another two dogs. The renal lesions produced were similar to those observed in naturally occurring primary cases although not sufficiently extensive to produce obvious malaise or nitrogen retention in the dogs infected. It is suggested that loss of virulence of the organism in vitro is the main reason for the inability to produce renal failure. Despite the lack of severity of the condition produced in the dog the cellular infiltration was characteristically mononuclear and showed a definite tendency to localise in the boundary zone. Spirochaetes were readily demonstrated in the kidneys.

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Appendix 1

Age incidence of Leptospira canicola infection in dogs.

Table 21

The age distribution of cases in the primary renal stage

Age	No. of cases		
	Mild	Severe	Most Severe
4-6 months	5	7	9
7-9 months	8	16	9
10-12 months	3	34	9
1½ years	4	10	14
2 years	7	14	12
2½ years	1	2	1
3 years	1	10	10
4 years	2	0	3
5 years	0	5	1
6 years	0	0	0
7 years	0	1	1
	31	99	69

Total 199

Unknown 23

Table 22

The age distribution of cases in the secondary renal stage.

Age	No. of cases Without Uraemia	With Uraemia
4-6 months	1	10
7-9 months	0	5
10-12 months	4	5
1½ years	4	3
2 years	7	7
2½ years	0	3
3 years	6	7
4 years	8	6
5 years	5	11
6 years	3	3
7 years	4	1
8 years	0	6
9 years	5	4
10 years	4	5
over 10 years (including 1 of 17 years)	9	11
	60	77

Total 137

Unknown 10

Appendices 2 to 6.

In these appendices are shown the serological, biochemical, urinary and relevant clinical findings of all 369 cases in the series. As the same method of presentation is used for each group, notes are given at this point to explain the headings and symbols used. Pages have been made to face each other so that the details of each case might be examined more readily.

Symbols

±, +, ++, +++, ++++ = positive to a varying degree.

\- = negative or absent.

Where an examination has not been carried out the space is left blank.

L. C.

In this column the reciprocal of the titre dilution against L. canicola is expressed as a whole number.

L. I.

Similarly the reciprocal of the titre dilution against L. icterohaemorrhagiae is expressed as a whole number in this column.

Blood urea

Values for blood urea levels are given as mg./100 ml.

Leptospiruria

This column shows the result of the dark ground examination of a drop of uncentrifuged urine.

Proteinuria

Any figures in this column represent a proteinuria expressed as mgm./100 ml.

Apathy

- = normal behaviour.
+ = slightly apathetic.
++ = markedly apathetic.
+++ = almost moribund.

Appetite

++ = normal appetite.
+ = eating approximately half the normal amount.
± = taking an occasional mouthful.
- = not eating anything.

Thirst

- = normal.
+ = noticeable.
++ = marked thirst.
+++ = indicates that the main preoccupation is with drinking.

Pulse

A full pulse describes an increased force or "volume" of pulse wave with little or no apparent loss in the natural elasticity of the artery.

On the other hand a hard pulse denotes a loss of arterial elasticity accompanied by increased force of the pulse wave.

A weak pulse indicates a marked fall in the pulse force or "volume".

Appendix 2

Mild primary renal stage.

38 cases.

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
75	13.11.47	3,000	300	35.4	
	20.11.47			27.3	
109	1.12.47	-	?10	18.8	-
	14.12.47	10,000	100	28.6	-
	17.12.47			25.6	-
127	9.12.47	3,000	300	26.2	+
	12.12.47				+
	3.12.51	100	10		-
131	9.12.47	3,000	100	21.4	
248	9.4.48	3,000	100	32.4	-
290	8.6.48	30,000+	10,000	43.4	-
	18.6.48	30,000	3,000	41.1	
331	10.8.48	10,000	100	23.4	-
337	17.8.48	1,000	300	24.2	+
	20.8.48	10,000	300	19.8	-
340	20.8.48	3,000	1,000	39.5	+
	11.10.48	3,000	300	48.2	-
	25.4.49	300	100	29	-
	10.10.49			43.4	-
	20.11.51	300	30	48	-
407	4.10.48	3,000	100	29.6	-
	4.5.50	3,000	100	28.9	-
	19.11.51	1,000	100	44	-
450	13.4.49	10,000	100	20.2	-
	14.4.49			24.4	-
	15.4.49	3,000	300	22.4	-

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
±	+					
-	-	+	-		104	150
±	-	++				
±		±	±	±		Hard
+	-	-	-	+++	102	170
		-	+		102	140
		-	++	-	101	
		-	-	-	102.5	Full 100
+	-	Para-plegic	++	-		
		+	±	Polyuria +++		
		+	-	++	105.6	144
		+	Emesis −	++	103.4	Full 150
		-	++	±	101	120
±	+					
±	+					
100	+	-	++	-	104	Hard 130
±	-	++	±	-	101.6	120
+	++	-	++	-	101	120
30	+	-	++	-	101.2	120
+	+	-	++	-	100.5	140
+	-	-	++	-		
±	+	-	++	-		

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
	16. 4. 49	3,000	1,000	40. 2	-
	19. 4. 49			15. 9	
	22. 4. 49	3,000		19. 8	-
	26. 4. 49	3,000		29. 2	-
	29. 4. 49	3,000		17. 4	-
	4. 5. 49	3,000	1,000	25. 1	-
	5. 5. 49	3,000	3,000	23. 0	
	6. 5. 49	3,000	1,000	23. 6	-
	9. 5. 49	3,000	1,000	26. 4	-
	11. 5. 49			29. 8	-
	20. 6. 49			24. 5	-
	21. 6. 49				-
	27. 6. 49	1,000	100	27. 2	-
	12. 7. 49	3,000	100	20. 2	-
	8. 8. 49			21. 2	-
	29. 8. 49				-
	21. 9. 49			26. 7	-
	14. 10. 49	3,000	300	22. 2	-
	7. 11. 49				-
	26. 1. 50	300	30	25. 1	-
452	14. 4. 49			21. 8	-
	16. 4. 49	3,000	1,000		-
	19. 4. 49	3,000		26. 2	-
	30. 4. 49	3,000	100		-
	19. 5. 49	3,000	100	22. 4	-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
±	+	-	++	-		
±	-	-	++	-		
+	+	-	++	-		
+	+	-	++	-		
±	+	-	++	-		
±	+	-	++	-		
±	+	-	++	-		
±	+	-	++	-		
±	-	-	++	-		
±	-	-	++	-		
±	+	-	++	-		
±	+	-	++	-		
±	+	-	++	-		
±	+	-	++	-		
±	+	-	++	-		
±	+	-	++	-		
±	+	-	++	-		
+	+	-	++	-		
±	+	-	++	-		
±		++	±	-	104	
±						
±						
±		-	++	-	101.5	110

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
545	15. 2. 50	30,000	1,000	18	+
	23. 5. 50	10,000	1,000	19. 8	-
	23. 11. 51	3,000	300	23	-
550	14. 3. 50	10,000	3,000	23	+
	15. 3. 50			23	
	16. 3. 50				+
	22. 3. 50	30,000	1,000	31. 2	+
	3. 5. 50	3,000	300	38. 4	-
579	9. 11. 49	30,000+	3,000	48. 7	+
	14. 11. 49	30,000+	3,000	27. 2	-
A30	24. 3. 50	3,000	100		+
	28. 3. 50	3,000	100	32. 8	
A51	29. 4. 50	3,000	300	35. 7	-
	27. 5. 50			35. 5	-
A216	17. 8. 50	3,000	100	29. 6	-
A619	15. 5. 51	30,000	1,000	30	+
	16. 5. 51				+
	18. 5. 51				+
	22. 5. 51				-
	29. 5. 51	30,000	3,000	29	-
	12. 6. 51	30,000	1,000	27	-
	29. 8. 51			18	-
A715	23. 7. 51	30,000	10,000	44. 5	-
A755	22. 8. 51	30,000	3,000	27. 2	+
	30. 8. 51			29. 2	
	27. 9. 51			31	-
	5. 12. 51	1,000	100	30	-

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
+	+					
±	-					
70	+	-	++	-	101.2	130
±	-	-	++	-		120
±	+	-	++	+		120
+	+	Fits				
±	-	++	-	++	103	Weak 130
±						
+						
±	+					
±	-					
+	+			++		
10	+	++	-	++		
20	+					
20	+					
±	-	-	++	-	103	Full 110
±	-	-	++	+		
30	+	-	++	-	103	Hard 130
70	+	++	Emesis —	+	101	120
60	-	-	++	Polyuria ++	102.4	Full
15		-	++	-	101.6	150
±	-					

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
A795	28. 9. 51	10,000	1,000	21. 3	+
	5. 10. 51			30	-
A814	5. 10. 51	30,000+	10,000	22	+
	9. 10. 51				-
A901	10. 11. 51				+
	29. 11. 51	30,000	1,000	27. 5	-
2X	28. 6. 49	10,000+	100	32. 9	+
15X	6. 9. 49	10,000+	300	35. 9	+
	9. 9. 49				+
	10. 9. 49				-
	12. 9. 49				-
31X	17. 1. 50	10,000+	-	37. 1	-
35X	14. 2. 50			33. 3	-
	20. 2. 50			29	-
	24. 2. 50	10,000	1,000	30. 3	
	3. 3. 50	1,000	300		-
	31. 3. 50	1,000	300	27. 9	-
	30. 11. 51	100	10	32	-
Z118	27. 11. 48	10,000	100	43. 6	+
Z157	31. 12. 48	10,000	300		+
	4. 1. 49	10,000	300	15. 4	+
	6. 1. 49			20. 9	-
Z181	17. 1. 49			35. 7	+
	20. 1. 49	10,000	-		-
Z222	5. 2. 49	10,000	100	43	+
Z230	8. 2. 49	10,000	-	47. 2	+
Z322	5. 4. 49	10,000	-	44. 6	

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
25	-	+	++	Polyuria ++	101.5	Full
±	-	-	++	-	101.6	
10	-					
10	+	-	++	++	101.5	Hard
110	+	-	++	-	101.5	
±	+	++	±			
+	-	++	-	+	104	Hard
++	-	+	±		101.8	
++	+	-	+	-	101.5	
+	+					
++	-					
±	++	++	-	++	101	Full
+	-	+	++		102.2	
±	+	-	++			
±	+	-	++			
+	++	-	-			Hard

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
64	10.11.47	-	-		
		Blood culture +ve			
	28.11.47	30,000	1,000	27.5	+
	11.12.47	10,000	300		+
	18.12.47				+
	1.3.48	1,000	10	22.6	
	13.12.48	300	10	33.7	-
	19.11.51	300	30	37.5	-
386	29.4.48	-	-		-
		Blood culture +ve			
	2.10.48	3,000	30	31.2	
	14.12.48	300	30	26.5	
	19.5.49	300	30	20.7	
	31.5.49	300	30		
	28.10.49	300	30	15.6	-
	18.11.51	100	10	38	-
455	30.4.49	-	-		-
		Blood culture +ve			
	13.5.49	3,000	100		+
	30.5.49	1,000	100	29	-
	2.11.49	300	30	25.5	-
Z9	18.10.48	-	-		
		Blood culture +ve			
	22.10.48				

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
		+	-		102	130
±	-	-	++	-		
±	-	-	++	-		
±		-	++	+	102.5	150
			++	+		
		-	++	-		
30	+	-	++	-	102	Hard 150
-	-	++	Emesis	-	105	110
		-	++	-		
		-	++	-		
		-	++	-		
±	-	-	++	-		
±	+	-	++	-		
20	+	-	++	-		Hard 120
±	+	++	-	-	104	140
±	-	-	+	+		
±	+	-	++	-		
		++	-	-	105	Full 120
		±	++	-	101.5	120

Appendix 3

Severe primary renal stage.

112 cases.

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
43	2.11.47	3,000	100	98.2	-
	10.11.47			70.8	
82	10.11.47			94.8	
	17.11.47			143	
	28.11.47	30,000	1,000	79	
104	21.10.47			50.6	
	30.10.47			49	
	27.11.47	30,000	300	75.2	-
	27.4.49	1,000	30	21.5	-
	9.5.49				-
	22.11.49			35.7	-
	26.11.51	300	30	73.5	-
105	10.11.47			94	
	28.11.47	10,000	1,000		-
110	12.12.47	10,000	100	56	
	18.12.47	30,000	1,000		
115	2.12.47	-	-	16	-
	16.5.49	30,000+	300	37.3	-
	30.5.49	30,000	1,000	74.6	-
	7.6.49	3,000	300	39.7	-
	28.11.49	1,000	-	47	-
	2.12.49			78.8	-
	15.12.49				-
129	9.12.47	1,000	100	140	-
	18.12.47	3,000	300		

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
+		++	-	++	103.5	Full 100
		-	++	+		
		++	±	++		
		-	±	+		
+	±	-	++	-	101.5	100
+	+	-	++	-		
+	-	-	++	-		
++	+	-	++	-	101.5	Hard
20	++	-	++	-		130
		++	-	++		
+	+					
		-	++	-		
±	-	-	+	Polyuria ++	102.2	100
±	-	+	+	Polyuria ++		
++	+					
±	-			Polyuria ++		
++	+					
++	+					
+	-					
		++	+	-	102	Full 90
+	+	-	++	-	101.6	Full 160

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
151	21.1.48	100,000	1,000	120	+
	4.12.51	30	10	109.5	-
179	11.2.48	3,000	300	37.9	+
	24.2.48	30,000+		56.4	
	28.5.49	100	10	39.5	-
	27.10.49			63	-
	7.3.50	100	30	57.1	-
	4.7.50	100	30	54.6	-
	2.3.51	100	10	59.7	-
	12.11.51	30	10	84	-
194	21.2.48	10,000	-	106.4	+
204	26.2.48	30,000+	300	78.8	-
	4.6.49			40.3	-
	24.11.51	300	30	83	-
212	7.3.48	30,000+	10,000	183.2	+
	15.6.48	1,000		36.2	
	15.2.49	300	100	47.7	-
	17.11.49	300	30	37	-
	6.2.50	300	30	25	-
	29.11.51	300	30	32.5	-
218	12.3.48	30,000	100	37.2	+
	6.4.48	3,000	300	30.8	
	7.6.49	300	-	53.2	-
270	10.5.48	30,000	100	27.1	+
	18.5.48	30,000+	1,000	53.6	
	23.5.48	30,000+	1,000	39.4	

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
+	+	++	-	++	100.2	Full 160
		-	++	-		Full
		+	Emesis ±	++		
		++	Emesis —	-		
±	+	-	++	-		
±	-	-	++	-		
±	+	-	++	-		
+	+	-	++	-		
200	++	-	++	-		
60	+	-	++	-		Full 130
		++	-	++	104.5	120
		++	Emesis —	++	102	120
+	-	-	++	-		
300	++	-	++	-		
		++	-	++	101.5	150
±		-	++	-		
+	+++	-	++	-		
+	+	-	++	-		
20	++	-	++	-		
		+	-	++	104	Weak
		-	++	-		
		++	-	-	105	
		-	++	-		
		++	-	-	104.5	Weak 130

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
276	18.5.48	10,000	100	38.6	-
	4.6.49	1,000	30	43.4	-
	26.11.49	300	-	53.4	-
	19.11.51	1,000	100	44.5	-
282	1.6.48	30,000	10,000	116	+
	28.6.48			44	
	2.6.49	1,000	300	64.4	-
	21.11.49			64.6	-
307	24.6.48	30,000+	300	44.3	+
	6.7.48	30,000+	300	46.5	-
	13.10.48	10,000	300	166	-
	2.11.48	3,000	100	24.7	-
	27.9.49	300	100	78.8	-
	30.11.51	30	10	93.5	
311	29.6.48	10,000	1,000	64.6	+
	6.7.48			40.8	-
327	3.8.48	30,000+	3,000	45.2	+
	24.8.48	10,000	1,000	48.6	+
	4.12.48				-
	11.1.49	3,000	100	35.8	
	18.5.49				-
	6.12.49	300	30	52.3	-
	7.6.50	300	30	43.1	-
	10.11.50	300	30	46.6	-
	25.4.51	100	10	38.8	-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
±	+	-	++	+		Hard
±	+	-	++	-		
10	+	-	++	-		
		++	±	++		
±	+	-	Emesis ++	+		Hard
±	+	-	Emesis ++	-		Hard 120
		++	-	++	102	Full 90
++	+	-	++	-		Full
+	+	-	++	-		
		++	-	++	102.4	Full 130
		+	+	-		
25	++	-	++	-		

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
329	6.8.48	30,000	30	27.2	+
	17.8.48	10,000	100	49.8	+
	12.10.48	3,000	10	98.4	
357	1.9.48	10,000	300	70.8	-
362	7.9.48	3,000	100	81.8	-
366	9.9.48	10,000	300	65.2	+
	15.9.48	10,000	300	62.2	+
	14.10.48	30,000	100	49	
367	12.9.48	3,000	300	51.2	+
	14.9.48			163.2	+
	16.9.48				-
	21.9.48	3,000+	300	122.8	-
	29.9.48	3,000	300	46.8	+
	13.10.48	10,000	1,000	144.4	-
	25.4.59	300	100	106	-
372	14.9.48	3,000	300	29.2	+
	21.10.48	10,000	1,000	52.6	
	13.12.48	1,000	100	51	-
376	16.9.48	10,000	100		
	12.10.48	10,000	1,000	79.6	+
395	28.9.48	3,000	100	146.8	
	31.9.48				-
	12.10.48	30,000	1,000	174	
	2.11.48	10,000	300	21.4	
	6.4.49	300	10	93	-
	13.7.49			49.7	
	7.10.49	300	-	40.1	-

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
		++	Emesis —	++		
		++	-			
		++	-	++	103.5	Weak 150
		++	Emesis —	++	103	
		-	++	-		
		++	Emesis —	++	104	Fast
		++	-	++	100.5	
		-	+	+		
		-	++	-		
+		++	-	++	102	Hard 140
		-	++	-		Hard
		++	-	-	103.8	
		+	+			
		++	-		103.8	
+		-	++	-		
		++	-	++		
±		++	-	++		
		±	+	+		
		-	++	++		
+	-	++	++	-		
±	++	-	++	-		

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
399	29.9.48	30,000	3,000	123.6	+
	13.10.48	30,000	3,000	58.4	
	27.4.49	1,000	100	50.2	-
	19.11.51	1,000	100	42	-
421	9.10.48	10,000	1,000	69.4	+
	19.10.48	10,000	3,000	52	-
	26.10.48				+
	4.11.48	30,000	3,000		+
	9.11.48				+
	13.11.48	30,000	3,000	131.2	-
	29.12.48	30,000	300	85.4	-
	1.3.49	300	30	61	-
	5.5.49	300	100	51.2	-
	3.8.49	300	30	38.9	-
427	15.10.48	30,000	1,000	108	+
	19.10.48	30,000	3,000	124.8	+
	28.10.48			156.5	-
	3.11.48	30,000	1,000	52	+
	11.5.49	1,000	30	70	-
428	6.10.48	10,000	1,000	54	+
	3.11.48	30,000	1,000	34	
441	29.12.48	3,000	100		
	30.12.48			108.8	-
	3.1.49	3,000	30		-
	4.1.49	3,000	30	104	-
	6.1.49	3,000	30	58.2	-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
+		++	Emesis —	++	102	130
		+	+	+		
±	+	-	++	-		
90	+	-	++	-	102.8	120
		++	-	++	102.5	Full
		-	++	-		
		-	++	++	102	
		-	++	-		
		-	++	-		
++	+	-	++	-		
+		-	++	-		
+	+	-	++	-		
+	++	-	++	-		Hard
		+	-	++	103.8	Full 120
		+	+	+		
		-	++	-		
		-	++	-		
±		+	-	++		
	-	++	++			
+	-					

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
470	25. 5. 49	3,000	100	57. 2	-
	26. 5. 49	1,000	30	41. 4	
	28. 5. 49	1,000	100	43. 8	-
	30. 5. 49	1,000	30	51. 2	-
	31. 5. 49				-
	18. 6. 49	300	100	32. 6	
492	8. 8. 49				-
	11. 8. 49	1,000	300	147. 6	+
494	25. 8. 49	3,000	300	36. 4	+
	29. 8. 49				+
	2. 9. 49	10,000	100	29. 3	+
	5. 9. 49				+
	7. 9. 49				+
	12. 9. 49	10,000	100	20. 9	+
	16. 9. 49	30,000+	1,000	41. 1	+
	21. 10. 49	30,000+	3,000	37. 9	+
	16. 11. 49			57. 3	-
	21. 11. 49			36. 6	-
495	26. 8. 49	1,000+	-	54. 2	+
	2. 9. 49	10,000	100	63	+
	5. 9. 49				+
	7. 9. 49				+
	15. 9. 49	30,000	1,000	54. 2	+
	20. 9. 49	30,000	1,000	72. 4	+
502	4. 10. 49				+
	5. 10. 49	30,000	100	51. 2	

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
±	+	-	++	-	101.5	Full 140
±	+					
±	-					
+	-					
±	+					
+++	+					
±	-	++	+	++		
±	++					
±	+					
±	-					
±	+	++	Emesis —	++		
±	+	-	++	-		
+	-					
±	-					
±	+	++	-	++		
±	+					
±	-					
±		-	++	++		
±	-					
±	+	++	-	-		Full 110
±	+	-	++	-		

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
	21.10.49	30,000	100	25.2	
505	11.10.49				+
	17.10.49	30,000+	300	148.8	-
	25.10.49	30,000+	300	59.8	+
509	22.10.49			84.9	-
	24.10.49				-
	17.11.49	3,000	300	30.3	+
	18.11.49			43	-
513	4.11.49	3,000	100	184	-
514	20.10.49	1,000	300	76.4	-
	4.11.49	1,000	300	85.2	-
	19.11.49	3,000	-	130.8	-
520	9.9.49	3,000	-	160.8	-
	15.9.49	10,000	-	70.4	-
	27.9.49			40.6	
	25.10.49	3,000	-	29.5	+
	22.11.49			24.2	+
	9.1.50	10,000	100	35.1	-
	21.11.51	100	10	39	-
529	23.12.49	10,000	1,000	58	+
	27.12.49	30,000	3,000		-
544	18.1.50			73.2	+
	3.2.50			32.3	+
	11.2.50	30,000+	1,000	47	-
	18.2.50				-
	31.3.50	30,000	300	46.4	

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
		++	++	-		
±	+					
+	+	-	++	-		Full
±	++	++	-	-		Full 110
±	-	+	+	-	101.5	Full
±	+	-	++	+		
+	++	Fits				
±	+					
±	+	+	±	-	104	Hard 100
+		-	++	-		Hard 120
±	+	-	++	-		Hard
+	+++					
±	+					
		-	++	-		Hard
±	-					
±	+	-	++	-		Hard
30	-	-	++	-		120
±	+	+	Emesis —	++	103.5	Full
+	+	-	++	-		
±	-	+	+	-	101.5	Hard
±	-					
++	-	-	++	-		
±	+					

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
552	18. 5. 50			57. 5	+
	24. 5. 50	30,000+	10,000	57	
	2. 6. 50				-
	12. 6. 50	10,000	300	44. 6	+
	22. 6. 50	10,000	1,000	51	-
	17. 7. 50	3,000	-	37. 7	
	29. 8. 50	100	10	28. 1	-
	10. 7. 51	300	10	33	-
560	27. 10. 50			92. 8	-
	4. 11. 50	30,000+	1,000	45. 1	-
	13. 11. 50	10,000	30	39. 5	-
580	10. 11. 49	30,000+	3,000	53	+
	16. 11. 49			34. 9	-
A8	27. 2. 50			65. 6	+
	6. 3. 50	30,000	3,000		-
	14. 3. 50				-
	3. 5. 50	1,000	100	53	-
	7. 6. 50			40	
	13. 12. 50			58	-
	7. 3. 51	100	10	33	-
	1. 8. 51	30	10	41	-
A40	2. 4. 50	30,000	1,000	194. 4	-
	23. 4. 50	10,000	300	124	
	4. 6. 50	1,000	100	124. 4	
	8. 5. 50			71. 6	-
A257	3. 10. 50	3,000	300	66	

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
+	−	+	+	+		
		−	+	++		
+	−	−	++	−		
±	+					
±	−					
		+	+			
+	+					
50	+	±	+	−	101.4	Hard 100
±	+	+	Emesis −	++	102	Full
20	−	+	+	+		Full 120
±	−	−	++	−		130
±	−					
+	+					
+	−	++	−	++		Full 100
±	−	++	±	−		
±						
±	+					
		−	++	+		Full
±	−					
±	−	±	+	++		Hard
25	−	±	++	+	101.6	Hard 115
+	+					
+	−					

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
A289	20.10.50	10,000	1,000	116.4	+
	23.10.50	10,000	1,000	146.4	-
	1.11.50			84.4	-
	14.11.50	3,000	30	28.5	-
A334	14.11.50	3,000	30	59.2	+
	21.11.50			45	-
	23.11.50	3,000	30		+
	7.12.50	1,000	-	33.8	-
A462	14.2.51	10,000	100	172	-
	19.2.51	30,000	1,000	186	
	26.2.51			110	-
	21.3.51			81.2	
A485	23.2.51			38.5	-
	2.3.51				-
	20.4.51			66.4	
	11.5.51	10,000	300	58	-
A549	30.3.51	10,000	3,000	52.1	+
	6.4.51	30,000+	10,000	57.4	-
	4.5.41	10,000	1,000		-
A561	10.4.51	3,000	300	188.8	
A566	11.4.51	10,000	1,000	79.2	
A627	18.5.51	1,000	30	57	-
	2.6.51	3,000	100	65.5	
	15.6.51	3,000	100	86	-
A703	17.7.51	30,000+	10,000	50	
	23.7.51	30,000+	10,000	52	-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
+	−	±	±	++	101	Full 140
+	++	−	++	++	101.2	110
10	−	−	++			
±	−	−	++	+		Hard 120
±	−	±	Emesis +	++	101.8	Hard
±	+					
±	+	−	++	−		
±	−					
30	−	++	Emesis −	++		
60	−	+	+	+	101.5	110
40	−					
		−	++	−	101	100
30	++	++	Emesis −	−		
40	+	+	+		103	
40	+					
40	+	−	++	−		Hard 120
20	−	±	Emesis +	−		
60	+					
10	−					
60	++					
		++	−	++		
10	+	+	+	+++		
10	+	−	++	++	101.6	Hard 110
±	+					
20	−	++	Emesis −	++	101.5	Hard

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
A718	21. 7. 51				-
	25. 7. 51	10,000	1,000	80	
	2. 8. 51			63	-
	20. 8. 51	3,000	300	76. 5	
A720	24. 7. 51	3,000	300	100	-
	25. 8. 51			91	+
	3. 9. 51			82	-
	25. 9. 51	3,000	300	100	-
A732	30. 7. 51	10,000	3,000	79. 5	-
	7. 8. 51	10,000	3,000	52	-
A751		30,000+	3,000	61. 3	-
				58. 1	
A769	10. 9. 51			38. 5	+
	19. 9. 51	30,000	1,000	56	-
A789	25. 9. 51	30,000	3,000	53	+
	4. 10. 51			31	-
	10. 10. 51				-
A793	27. 9. 51	10,000	3,000	53	+
	5. 10. 51			50. 5	-
A801	1. 10. 51	30,000+	3,000	129	+
A825	10. 10. 51	10,000	300	50	+
	18. 10. 51			70	-
A831	12. 10. 51			64	+
	23. 10. 51	10,000	300	103	-
A838	18. 10. 51	3,000	300	140	-
	25. 10. 51			59	-

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
50	+					
70	+					
100	+	+	-	+	102.4	Full 120
50	+					
40	-					
50	-					
20	+	++	Emesis -	+++		Full 130
±		-	++		102.2	Normal 108
30	+					
40	-					
±	-					
		-	±	++		
±	-	-	++	-	101.2	Full
70	+					
10	-	+	+	++		
25	-	-	++		100.8	Full 88
70	-	+++	Emesis -	Polyuria ++	104.2	Full 120
60	-	+	Emesis ±	++	102.2	Full
30	+	-	++		103	120
50	+	++	Emesis ±	+++	101.2	Hard 140
30	++				102	160
40						
30						

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
A840	19.10.51	3,000	1,000	175	-
	25.10.51			64	
A848	22.10.51	10,000	300	32	+
	30.10.51			34	-
	26.11.51	10,000	1,000	52	-
A852	26.10.51			49.5	+
	3.11.51			121	-
	9.11.51			121	
	16.11.51			96.5	-
	30.11.51	30,000	3,000		-
A874	5.11.51	10,000	100	112	-
A883	8.11.51			68	+
	9.11.51	10,000	1,000	64.5	
	26.11.51	30,000+	3,000	51	-
A962	12.1.52	10,000	300	91.5	+
	18.1.52			91.9	-
	16.2.52			84.5	-
4X	19.7.49	10,000+	100	58.6	
5X	22.7.49	10,000+	100	143.2	+
	30.11.51	1,000	100	53.5	-
6X	28.8.49	10,000+	300	184.8	+
7X	29.7.49	10,000+	100	135.6	+
	2.8.49	10,000+	300	168.4	-
	10.8.49			92.4	+
	18.8.49			101.2	-
	31.8.49	10,000	100	69.4	-
	15.10.49	3,000	100	98.6	-

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
10	+					
20	-	+	+	++	101.2	
±	-	-	++	-	101.3	120
±	++	-	++	++		Hard
10	-	+	+	++		Hard
+	-					
20	-					
±		-	++	++		Normal
30	-					
20	+					
99						
50	+	-	++	-		80
82	+					
20	-					
60	+					
				++		
±	-	++	Emesis —	++	101	Slow Weak
250	+	-	++	-		
+	-	++	Emesis —	-	102	120
+	-	++	Emesis —	++		
±	-					
±	-					
+	-					
+	+					
+	-					

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
8X	12. 8. 49	3,000	100	41. 8	+
	25. 8. 49	10,000+	300	61. 6	+
11X	15. 2. 49	10,000	300	85. 2	-
	23. 11. 49	100	10	40. 5	-
12X	24. 8. 49			131. 6	-
	30. 8. 49	10,000+	100	27. 7	-
	5. 9. 49	10,000	100	32	-
	20. 9. 49	10,000	100	25. 4	-
13X	1. 9. 49	10,000+	300	184	-
	5. 9. 49	10,000	300	49	-
14X	2. 9. 49	10,000	100	88	+
	5. 9. 49	10,000	300	60	-
	20. 9. 49				-
15X	14. 9. 49				-
	21. 9. 49	10,000	100	68	-
17X	7. 11. 49	10,000	100	174. 5	-
	27. 4. 50	100	10		-
25X	26. 11. 49	10,000	-	47. 4	+
	7. 12. 49	10,000	-	60. 2	-
	15. 12. 49			35. 4	-
26X	29. 11. 49	10,000	30	99. 4	-
	2. 12. 49				-
	3. 1. 50			48. 5	-
28X	16. 12. 49	10,000+	1,000	37. 7	+
	27. 12. 49				+
	31. 12. 49				+

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
±	-					
±						
+	+	++	-	++		
500	++	-	++	-	101	Hard 120
+++	++					
++	+					
±	+					
+	-					
±	++	++	-	-	101.5	Normal
±	+	-	++	-		
±	++	++	-	+	101.5	110
±	+	-	++	-		
±	+					
±	+					
±	+					
+	+	+	Emesis +	++		Hard
±	-	+	Emesis -		102	
±	-					
+	-	-	++	-		
+	++					
+	+	-	++	++		Hard
+	-					
+	-	++	Emesis -	++		
	+					

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
	5.1.50	10,000	100	100.6	-
29X	5.12.49	30,000	-	56.8	
	7.12.49				-
	15.12.49	10,000	-	63	+
	23.12.49	10,000	-	74.4	-
	31.12.49				-
	9.1.50	3,000	-	76.2	-
	16.1.50	3,000	-	53.1	-
	20.2.50			97.2	-
34X	6.2.50	30,000	1,000	49.6	-
	25.2.50			56	-
	6.3.50	10,000	1,000	37.8	-
Z20	25.10.48	30,000	100	150	+
Z23	25.10.48	10,000	100	131.2	-
Z27	27.10.48	10,000	1,000	114.4	+
Z32	28.10.48	10,000	100	150	+
Z39	1.11.48	10,000	1,000	74	+
Z46	17.11.48	10,000	-	162.8	+
Z53	6.11.48	10,000	-	57	+
Z87	17.11.48	10,000	300	79	+
Z88	17.11.48	10,000	1,000	159.6	+
Z106	23.11.48	10,000	100	147.5	+
Z127	2.12.48	10,000	100	183.2	+
Z134	7.12.48	10,000	100	72.2	+
Z152	23.12.48			146	-
	27.12.48	10,000	100	95.2	
	15.1.49				+

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
+	+					
±	-					
±	-					
±	+					
±	-					
±	-	-	++	-		Hard
±	++	-	++	++		
++	+					
+	±	-				
±						
±						
+						

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
Z156	30. 12. 48	10,000		116. 8	+
	4. 1. 49	10,000	-	93. 6	-
Z183	17. 1. 49	10,000	300	105. 6	+
		10,000	100	43. 1	
Z195	24. 1. 49	10,000	100	143. 2	-
Z229	8. 2. 49	10,000	300	74. 8	+
Z294	15. 3. 49	10,000	100	130	+
	4. 3. 50	300	30	46. 7	-
	4. 4. 50	1,000	100	89. 4	
477	14. 6. 49				-
		Blood culture +ve			
	16. 6. 49	-	-		-
	18. 6. 49	10,000	1,000	53. 4	-
	26. 4. 49	30,000	1,000	78. 2	-
	8. 11. 49	1,000	30	60. 6	-
	18. 1. 50	300	30	33. 7	-
252	13. 4. 48	3,000	30	74	++
		Blood and urine cultures +ve			
	18. 4. 48				+
	23. 4. 48	30,000	300		+

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
+						
±						
+						
+						
±	+	++	-	-	104	120
±	+	±	+	-	102	
±	+					
±	+	-	++	-		
+	+	-	++	-		
±	+	-	++	-		
+	+	+	+	+	102	110
		-	++	-		
		-	++	-		

Appendix 4

Most severe primary renal stage.

72 cases.

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
17	22.10.47			415	
48	4.11.47	10,000	1,000	200.8	+
	6.11.47				+
	12.11.47	60,000	30,000	360	
52	5.11.47	3,000	300	96.4	+
	15.11.47			212.8	
	22.11.47			116.8	
	5.12.47	10,000	1,000	85.2	
	20.6.48	300	30	47.2	
	7.4.49	300	10	35.8	-
	20.11.51	300	30	54	-
143	20.1.48	30,000	3,000	400	+
150	22.1.48	30,000+	3,000	415	-
152	22.1.48	10,000	100	90	
	18.10.49	100	-	184	-
	21.10.49	100	-	235	
221	13.3.48	30,000	3,000	136	+
	7.4.48	3,000	1,000	120	
	2.5.49	1,000	1,000	417	-
	3.5.49				-
	4.5.49	3,000	3,000	447	-
	6.5.49			434	-
	7.5.49	3,000	1,000	592	
224		30,000	1,000	740	+
228	22.3.48	10,000	3,000	412	+
	26.3.48	300,000	3,000		

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
		Moribund				
		++	-	++	102	140
		+	+	++		
		Moribund			97.2	Weak 150
+	+	++	++		101.5	120
		-	++	-	101.5	Full 100
+	-					
		-	++	-		
10	+	±	Emesis ±	++		Hard 120
		++	-	++		
+	-	++	-	++	99.4	120
		-	++	++	101.2	120
		Moribund				
		++	±	++	103.8	Full 140
		-	++	+		
++	+	+	±	+++		Hard
+	+					
++	-					
		Moribund				
		Moribund			99	Weak
		++	-	++	101.1	120

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
236	30. 3. 48	30,000	300	313	+
242	2. 4. 48			450	+
	4. 4. 48	10,000	300		
268	10. 5. 48	30,000	3,000	320	+
	12. 5. 48			354	
	19. 5. 48	10,000	1,000	310	
272	12. 5. 48	30,000	1,000	178	+
	19. 5. 48	30,000	1,000	227	
	7. 6. 48			56. 6	
281	29. 5. 48	10,000	1,000	500	-
294	14. 6. 48	30,000+	100	256	+
	17. 6. 48	30,000+	1,000		+
	23. 6. 48			588	
299	17. 6. 48	3,000	10	58. 8	-
	25. 6. 48	1,000	10	39. 2	
	3. 8. 48	300	10	53. 8	
	14. 3. 49	300	-	129	
	17. 3. 49			174	
	23. 3. 49			196	
	28. 3. 49			157	-
	4. 4. 49	300	-	227	
	15. 4. 49			158. 4	
	16. 5. 49	300	10	193	
318	8. 7. 48	10,000	300	276	+
	24. 11. 51	300	30	51	-
323	14. 7. 48	10,000	1,000	230. 4	

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
		+	±	++	103.5	Full 150
		++	−	++	99.8	Weak 150
		Moribund				
		Moribund				
		Moribund				
		++	Emesis	++	102.4	Full
		Moribund				
			++	−		
		−	++	−		
		−	++	−		
		+	+	++		Hard
+						
+	+	++	−	++		
+	+	++	−	+++		
30	+	−	++	−		
		Moribund				

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
324	1.8.48	10,000	300	129.2	+
	10.8.48			295.2	-
	5.5.49	300	100	44	-
	24.11.51	100	10	47	-
332	10.8.48	3,000	100	390.4	-
344	23.8.48	10,000	1,000	228	+
	31.8.48	10,000	300	376	
358	31.8.48	1,000	-	382	+
	7.9.48	3,000	300	590	-
	11.9.48	10,000	300		
370	14.9.48	10,000	10,000	280	+
	17.9.48	10,000	3,000	91	-
	23.9.48			28.3	-
	11.10.48	3,000	1,000	45.7	-
	9.11.48	3,000	1,000	31.9	-
	12.4.49	300	100	31.4	-
	22.9.49	300	100	31.6	-
384	23.9.48	3,000	300	196	-
	28.9.48	10,000	100	380	-
408	4.10.48	3,000	30	442	-
419	7.10.48	3,000	1,000	396	-
422	10.10.48	30,000	3,000	289	-
	18.10.48	10,000	3,000	49.2	-
	21.10.48			94	-
	26.11.48	1,000	100	39.7	-
436	16.12.48	10,000	100	414	-
	17.12.48				-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature o F	Pulse
		++	-	++	102	Full 100
		-	++	-		
		-	++	-		
60	++	-	++	-		Hard 130
		++	-	++		
		++	-	++		
		Moribund				
		++	-	++	103.4	Full
		++	-	++		
		++	-	++		
		-	++	-		
±		-	++	-		
±	-	-	++	-		Hard
		-	Emesis ±	++	101.5	Full
		+	-	++	101	Full 180
±	-	++	Emesis ±	++	99.5	Weak 110
		++	Emesis -	++	101.5	Weak 120
		++	Emesis -	++	102.8	Full 120
		+	+	+		
		++	-	++		
		Moribund				
		++	-	++	101	Weak
±		Moribund				

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
439	3.1.49	30,000+	3,000	339	-
443	3.2.49	30,000+	1,000	335	+
445	23.3.49	10,000	100	215.5	
	28.3.49			166	-
	29.3.49			171.5	-
462	29.3.49	1,000	-	216	+
	4.4.49	10,000		333	-
	6.4.49	30,000	300	487	
467	21.5.49	10,000	-	139.6	
	25.5.49	3,000	10	324	-
	4.8.49	1,000	300	187.2	-
	13.9.49			450	-
	15.9.49	1,000	-	334	-
476	10.6.49	10,000	300	297	-
481	24.6.49	30,000+	100	200.2	
482	20.6.49	1,000	100	239	-
	25.6.49	3,000	300	390	-
487	3.8.49			500.1	-
	4.8.49	30,000	3,000		+
488	26.7.49			162.4	-
	5.8.49	30,000	1,000	335	-
489	9.8.49	30,000	100	840	-
497	15.9.49	10,000	100	127.2	+
	16.9.49	30,000+	3,000	292	+
499	30.9.49	30,000+	1,000	682	-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
		Moribund				
±	+	Moribund				
		++	-	++	101.5	
+	+					
+	-	++	-	++		
+	-	++	-	++	102	Full 120
		Moribund				
		++	-	++	103.6	Full 120
++	++					
++	++					
+++	+	Moribund				
±	+	++	Emesis -	++		Full
		++	-	++		
+++	+	++	Emesis ±	++		Full 125
+++	+	Moribund				
±	-	++	Emesis -	++		
+	-	Moribund				
±	+	++	Emesis -	++		
		±	+	++		
±	+	Moribund				
+	+	++	±	++	102.6	Full 90
++	+	Moribund			99	
++	++	Moribund				

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
501	4.10.49			248	+
	5.10.49	3,000	1,000	269	-
	17.10.49			90.5	
	10.10.49	3,000	1,000	144	-
	19.10.49	3,000	100	53	-
	5.11.49	3,000	100	32.2	
	20.1.50	300	100	32.6	-
	20.11.51	300	30	45	-
507	14.10.49			201	+
	17.10.49			286	-
	18.10.49	300,000+	10,000	618	-
515	5.11.49	10,000	-	303	+
521	28.11.49				+
	29.11.49	30,000	300	350	
	3.12.49				-
522	28.11.49	10,000	-	228	+
535	13.1.50	30,000	1,000	506	-
553	4.4.50	30,000	1,000	126.4	-
	12.4.50	30,000	3,000	232.8	-
	15.4.50				-
	17.4.50			166.5	-
	20.4.50	10,000	3,000	171.6	-
	2.5.50	10,000	1,000	148.8	
	31.5.50			156.8	-
	7.6.50	3,000	1,000	152	-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
+	+	++	Emesis −	++		125
+	+	+	+	−		
±	+	−	++	−		
±	−	++	±	++		
		−	++	−		Full
±	+	−	±	+		Hard
20	+	±	Emesis +		101.5	Hard 100
+	++	++	Emesis −	++	102.8	
++	++					
++	++	Moribund				
		++	Emesis −	++	101.8	
±	−	++	−	++	101	Weak 150
+	+++	Moribund				
+	−	++	−	++		
++	++	++	Emesis −	++	102.5	Normal 150
++	+	++	Emesis −	++	102	Full
+	−	+	+	++		
+	−					
++	+	+	+	++		Full
±	+					
+	+					
++	+	+	+	++		Full

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
559	24. 10. 50	1,000	100	337	-
	25. 10. 50			315	-
	26. 10. 50	10,000	1,000	295	-
563	6. 3. 51			293	-
	8. 3. 51	30,000+	3,000	221	
564	20. 3. 51			337	-
	22. 3. 51			403	
	23. 3. 51				-
	10. 4. 51			460	-
	13. 4. 51	30,000	1,000	582	-
565	26. 6. 51	30,000+	10,000	342. 4	+
	4. 7. 51	3,000	1,000	265	-
574	24. 5. 51	30,000	3,000	290	+
	30. 5. 51			367. 5	-
A51	12. 4. 50	1,000	300	252	+
	17. 4. 50	3,000	1,000	65. 2	-
	20. 4. 50	3,000	1,000	58. 6	-
A225	22. 8. 50	30,000+	10,000	260	-
	28. 8. 50	30,000+	3,000	380	
A307	30. 10. 50	3,000	1,000	236	+
	8. 11. 50			243. 5	-
	15. 11. 50	30,000+	10,000	712	-
A717	23. 7. 51	30,000	10,000	370	-
A784	20. 9. 51	30,000+	300	200. 1	+
	4. 10. 51			190	-
	22. 10. 51			164	

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
±	-	++	Emesis -	++	101.2	Full 140
+	+					
++	+	+	±	++		Weak
90	+++	++	Emesis ±	++		
		++	-	++	99	Weak 140
25	-	++	Emesis ±	++	101.8	Full 120
		+	-	++		Weak
40	+++					
20	-	+	++	-	99.2	114
120	++	+	Emesis +		101.2	Weak
50	-	++	-	++		
10	+	++	-	++		
100	-	++	Emesis -	++	101.5	Full
120	+	++	Emesis -	++		Weak 140
+	+	+	-	++	102.2	
±	++	-	++	-		
±		-	++	-		
+	-	++	Emesis -	++	1.1.5	Full
		Moribund				
+	+	++	-	++	101.5	150
70	+	±	Emesis ±	+	104	Weak 160
±	+	Moribund				
+	+					
10	-	++	-	++		
60	+					

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
A787	21.9.51	30,000	300	540	-
A798	28.9.51	10,000	3,000	213	-
	4.10.51			85	-
A818	8.10.51	30,000	3,000	91	+
	10.10.51				+
	16.10.51	30,000	3,000	350	-
	18.10.51			495	-
A819	6.10.51	100	30	162.5	-
	8.10.51	3,000	300	230	-
	16.10.51	3,000	300	81	-
1X	21.6.49	10,000+	100	226	-
	27.6.49			203	
3X	15.7.48	10,000	100	610	+
9X	10.8.49	10,000	300	304	
Z17	18.10.48	10,000	10	262.4	-
Z43	2.11.48	10,000	-	213	-
Z81	15.11.48	10,000	1,000	288	
Z176	14.1.49	10,000	-	252.8	
Z204	15.1.49	10,000	-	324	+
	27.1.49			356	
	28.1.49			265	
	29.1.49			330	
Z218	4.2.49	10,000	1,000	285	+
376	16.9.48	10,000	100		
		Blood culture +ve			
	12.10.48	10,000	1,000	219.6	+

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
1200	–	++	Emesis –	++		Full
160	+	+	Emesis ±	++		
70	+					
20	+	++	–	++		
40	+	++	Emesis ±	++	101	
10	–	+	++	+	101.8	Full 84
±	–	++	Emesis ±	++	102.2	Full
+	–	++	–	++	103	Weak 168
		++	–	–	103.8	110
+	+	+	±	++		

Appendix 5.

Secondary renal stage without uraemia.

66 cases.

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
98	25.11.47	30	-	21.6	
101	26.11.51	30	-	33.4	-
102	26.11.47	300	30	22.4	
145	20.1.48	300	10	35.8	
148	23.1.51	30	10	35.5	
166	2.2.48	1,000	30	35.3	
168	19.11.51	1,000	100	37	-
174	3.2.48	-	-	16.8	
	26.2.48	-	-	15	
	14.12.48	100	10	19.1	-
180	11.2.48	300	30	15.6	
188	20.2.48	300	30	30.6	
193	20.2.48	100	10	19.4	
207	4.3.48	300	-	18.6	-
	23.3.48			19.4	
	20.11.51	30	10	29.5	
210	3.3.48	100	-	47.2	
227	23.3.48	300	10	39.6	-
230	7.12.49	100	10	28.1	-
	11.12.49			21.8	-
243	6.4.48	300	100	35.6	-
	21.4.48	1,000	30	32.1	
250	9.4.48	300	30	27.4	-
	5.6.48			22	
	19.11.51			30	

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
+	+	++	+	++		
+		-	++		101.5	120
±	-	-	++	+	101.5	Hard 130
		++	-	++		
+++	+	++	++	+	100.4	120
		Moribund				
50	+	-	++	-		Full 110
		++	-	++	105	Full 100
±	-	+	+	+	103	
		Fits				
		++	-	++	101.5	110
		++	Emesis ±	++	102.6	Full
		-	Emesis ++	++	102.8	Full 120
		-	++	+		
		-	++	-		Hard 120
		++	Emesis -	++	103.6	Full 120
		-	++	-		
±	-	++	-	+		
±	+	+	+	-		
		++	-	++		
		++	-	++		
		++	-	+++		
		-	Emesis -	+++		
		-	++	+	101.5	Hard

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
257	15. 4. 48	100	30	32	-
	11. 3. 49	30	10	28. 1	-
	27. 10. 51			47. 5	-
	23. 11. 51	30	10	35	-
264	28. 4. 48	300	30	35. 6	
266	14. 5. 48	30	-	16. 8	
	3. 6. 50			39. 3	
	5. 6. 50	100	30	32. 4	-
289	7. 6. 48	30	-	22. 8	
295	14. 6. 48	300	30	39. 4	
301	17. 6. 48	300	-	29. 2	
	10. 3. 49	100	-	35. 4	
	4. 4. 49	300	-	40. 4	
	16. 1. 51	100	10	30. 5	-
	8. 6. 51	300	30	37	
	28. 11. 51	100	10	46	-
304	21. 6. 48	300	-	23. 5	
315	29. 6. 48	300	30	20. 7	
319	23. 8. 48	300	100	30. 9	-
	9. 7. 48	100	30	24. 9	
338	14. 8. 48	100	30	19. 4	-
349		100	-	25	
351	28. 8. 48	30	10	17. 4	
	9. 5. 49	30	30	35. 9	-
352	29. 8. 48	300	30	25. 8	
389	27. 9. 48	1,000	100	39. 3	-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
		++	±	++	102.6	Hard
±		++	-	++	102	120
		±	Emesis ±	+		
110	+	±	Emesis ±	+		Full 120
		+	+	++		
+	+	+	Emesis ±	++		
±	-	-	+	++		
		++	Emesis +	++		
		-	++	-		
		-	++	-		
		-	++	-		
+	++	-	++	-		
		++	+	-		
500	++	-	++	-		Hard
		++	+	++		
		++	Emesis -	++	104	Weak 100
		Moribund				
		++	-		101.5	Weak 90
		+	+	++		
+	+	Moribund				
		++	Emesis -	++		
		++	-	++	104.2	Hard 124

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
430	16.10.48	100	-	36.2	
449	9.4.49	100	10	21.5	-
461	12.5.49	300	30	44.8	-
	13.5.49	300			-
	16.5.49			44.8	-
468	27.4.49	300	30	20.2	-
	28.4.49				-
	29.4.49			15.2	-
	25.5.49	300	30	48.3	
	22.12.49			25.6	-
581	9.11.49	300	-	33.1	-
	10.11.49			31.8	
	21.12.49				-
A12	8.3.50	300	100	30.4	-
	18.3.50	100	10	40.7	-
A26	22.3.50	100	10		-
	1.5.50	100	10	36	
A36	30.3.50	1,000	10	33.6	-
A44	4.4.50	1,000	300		
	18.4.50				-
A50	7.4.50	300	100	26.9	-
A54	13.4.50	100	30	35.7	-
A176	6.7.50	300	100	27.5	-
	12.7.50	300	30	34.6	
A183	11.7.50	300	30	34	

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
		++	-	-		
+++	-					
++	-	++	-			
+	+					
±	+	++	-	+		
±	+					
±	-					
±	+					
+	+					
±	-					
+	+					
±	+	+	+	-	101.5	
±	+	-	++	++		
+	-	-	++	++		
		++	Emesis -	++		
+	-	+	-	++	-	
++	+	+	+	++		Hard
±		++	Emesis -	++		
		-	++	-		
		-	++	-		
		-	++	-		

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
A221	21. 8. 50	30	10	32	-
	24. 8. 50	300	30	27. 8	-
A228	25. 8. 50	300	100	31. 5	-
A236	5. 9. 50	100	10	31. 2	-
A238	12. 9. 50	100	10	28	
A329	9. 11. 50	300	30	28. 5	-
	7. 12. 50	100	10	42. 7	-
A421	17. 1. 51	1,000	100	27. 1	-
	26. 1. 51	300	30	21. 3	-
A474	19. 2. 51	100	30	33	
	21. 2. 51	100	30	38. 2	
	26. 2. 51	300	30	30	
	27. 2. 51	300	30		
A609	7. 5. 51	300	100	35. 5	-
A780	19. 9. 51	100	10	20	-
A794	27. 9. 51	1,000	100	31. 5	-
A809	2. 10. 51				-
	4. 10. 51	300	30	27. 5	-
A821	8. 10. 51	100	10	26	-
A823	9. 10. 51	1,000	100	37. 5	-
A839		1,000	100	37. 5	-
A849	23. 10. 51	100	10	33	
	24. 10. 51			20	-
A857	29. 10. 51	300	30	43	
12X	12. 12. 49	300	-	27. 7	-

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
±	+	++	−	+	101	Weak 150
+	+	−	++	−		
±	−	+	+	++		
++	+	+	Emesis +	−		
		+	Emesis +	+		
±	+	−	++	−		
±	−	−	++	−		
±	+	++	±	+		Hard
10	++	−	++	−		
100	+	+	+	++	101	150
		+	++	−	102.2	150
		−	++	−	102.2	150
200	−	−	++	−		
200	−					
10	−					
120	−					
40	+	+	+	++	106	Hard 89
30	−	−	++	++		
10	+					
	−					
10	−					
50	−					
±	+					

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
36X	9.12.49	100	30	32.8	-
	24.12.49			24.8	
	27.12.49				-
Z4	13.10.48	100	10	25.8	
Z6	18.10.48	300	100	27.2	-
Z22	19.5.49	100	-	28	-
Z24	26.2.49	300	30	35	-

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
±	++	++	Emesis −	++	101.5	
±	−					
+	+	−	++	−		
±	+	−	++	−		

Appendix 6

Secondary renal stage with uraemia.

81 cases.

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
46	4.11.47	100	10	137.8	
	8.11.47			313.6	
110	1.12.47	1,000	100	155.2	
142	19.1.48	1,000	30	58.8	
147	20.1.48	30	-	160	
155	27.1.48	1,000	300	79.6	
	3.2.49	30	10	114.8	-
	25.4.49	100	10	81.8	-
	6.1.50				-
159	28.1.51	30	-	244	-
162	28.1.48	100	10	420	
163	28.1.48	30	-	140.8	
165	2.2.48	1,000	100	43.4	
168	1.2.48	100	-	50.2	
	25.3.48	100	-	28.4	
	7.4.48	300	10		
	12.11.48			24.8	
172	2.2.48	300+	100		
	13.5.48				+
	13.12.48	100	10	51	-
	15.3.49	100	10	35.2	-
	27.7.49			38.8	
	26.10.49			32.1	-
	10.2.50	100	10	49.5	-
	3.10.50	100	10	47.5	-
	26.12.50				-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
	-	-	++	-	102	140
+		+++				
+	+	++	-		105	
		+++			99	Full 100
		++	-	++		
		++	-	++	103	Full 120
±	+	-				Full
±	+	-	++	++		Full 120
+++	++	+++			100	Weak 180
+	+	++	-	++		Weak
		++	-	++	102	Hard
		±	++	++	101	Hard 110
		++	-	++	102	Hard
		++	-	++		
		-	++	-		
		+	-	+++	103.5	Full 120
		-	++	-		
±	-					
+	+	-	++	-		
±	+	++	+			
±	+	-	++	-		Full
±	-	-	++	++		Hard
+	+	-	++	-		
+	+	-	++	-		

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
	23.1.51	100	10	33.2	-
	14.6.51	300	30	43.5	-
175	3.2.48	300	10	87.6	
	26.2.48	1,000	300	64	
	13.12.48	300	30	34.6	-
	6.6.49	100	? -	36.8	-
	21.11.49			36.2	-
177		100	30	291	
185	18.2.48	300	-	286	
190	20.2.48	100	10	190	
192	21.2.48	300	-	193	
195	23.2.48	100	10	127.2	
196	15.6.48	100	-	580	-
220	15.3.48	300	-	286	
	25.3.48	100	-		
226	22.3.48	100	10	147.2	-
232	27.3.48	30	-	326	
246	8.4.48	100	10	322	-
247	6.4.48	1,000	100	44.1	-
	19.11.51	300	30	100	-
269	11.5.48	1,000	100	369	-
279	25.5.48	100	-	200	-
	4.6.48	300	100	584	
284	2.6.48	1,000	300	465	-
291	10.6.48	1,000	100	124	
	14.6.48			155	

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
30	+	+	−		101.6	Hard
		+	−	+	104.8	Full
		−	++	−		
±	+	−	++	−		
+	+	−	++	−		Hard
		−	+	++	101.5	Hard 120
		+	+	++		
		++	Emesis −	++		
		++	−		103.5	Weak
		++	Emesis −	++		Hard 110
		+	+	++	101.5	Hard 120
		+++	−			
++	++	++	−	+		110
+						
		+++	−	++	100.8	Hard
±	−	−	−	−	102	120
60	+	+	+	++	101	Hard
		++	−	++	101.5	Hard 120
		−	+	+++	100.5	Hard 100
		Moribund +++				
		Moribund				

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
292	10. 6. 48	1,000	10	309	
293	12. 6. 48	300	-	265	
298	16. 6. 48	30	-	752	-
300	17. 6. 48	300	-	66. 4	-
	26. 6. 48	300	-	53. 2	
	3. 8. 48	300	-	66. 4	
	3. 3. 49	30	10	276	-
302	18. 6. 48	300	-	233	
	6. 7. 48	100	-	176	
360	6. 9. 48	100	10	333	-
364	9. 9. 48	30	-	75. 8	
390	27. 9. 48	100	30	80. 4	
	13. 3. 50	10	-	272. 5	
	20. 3. 50			390	
392	27. 9. 48	1,000	100	153. 2	-
393	28. 9. 48	100	-	102. 4	
397	20. 9. 48	100	10	50. 8	-
402	30. 9. 48	100	10	259	
406	4. 10. 48	100	-	291	-
409	7. 10. 48	100	10	368	-
423	11. 10. 49	300	30	227. 2	
426	15. 10. 48	1,000	10	108. 8	

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
		-	Emesis +	++	101.5	Hard 120
		+	Emesis −	-	101.4	Hard
		Moribund	Emesis	++		
		-	++	-	101.5	Full
+		++	±	++		
		++	-	++	101.5	Hard
		Moribund				
++	-					
		++	-		101.5	
		Moribund				
		++	-			
++		±	Emesis −	++	101	Weak 130
		±	Emesis ±	++		Full 120
+	++	-	++			
		Emaciated				

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
442	24. 1. 48	1,000	30	588	-
	25. 1. 48			660	-
444	18. 3. 49	30	10	476	-
471	24. 5. 49	100	30	480	-
	26. 5. 49			664	-
483	29. 6. 49	300	30	92	-
510	8. 9. 49				-
	29. 10. 49	300	30	1 30. 1	
547	10. 3. 50	300	100	42. 6	-
	4. 4. 50	300	100	139. 1	
567	22. 1. 51			53. 2	-
	13. 6. 51			150	
	25. 6. 51	30	10	100	-
573	8. 5. 51			36. 5	-
	17. 5. 51			100. 5	
	23. 5. 51	300	30	148	
A11	7. 3. 50	100	30	152	
A33	25. 3. 50	100	30	74. 8	-
	31. 3. 50	100	30	117. 2	-
A37	30. 3. 50	300	100	124	-
A70	25. 3. 50			161. 5	
	20. 6. 50	30	10	260	

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
		++	Emesis −	++	100	Weak 100
		Moribund				
++		++	Emesis −	++		Hard
++	−	++	Emesis −	++	100	Hard
+	−	Moribund				
		++	−	++		
+	+					
±	−					
±	+	++	Emesis −	++		
		Fits				
120	−	+	+	++		
60	−	+	Emesis +	++		Hard 100
60	−					
+++	++	++	−	++	104	
++	+					
+++	+++					
		++	−	++		
++	+	++				

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
A80	5. 5. 50	300	10	80. 4	-
	12. 5. 50			75. 4	
	17. 5. 50	30	-	100. 4	-
	19. 5. 50			56. 2	-
A92	12. 5. 50	30	-	322	-
A237	19. 9. 50	300	30	300	-
A260	5. 10. 50	30	10	541	
A270	7. 3. 51			88	-
	22. 6. 51	300	30	96	-
	20. 11. 51	100	10	415	
A340	15. 10. 50			223	-
	22. 11. 50			232	-
	27. 11. 50	30	10	288	
	4. 12. 50	300	100	282	-
A585	24. 4. 51	30	10	405	-
A771	12. 9. 51	300	100	182	-
	19. 9. 51			165	-
	27. 9. 51			210. 5	-
A775	13. 9. 51	100	30	467	-
A813	5. 10. 51	1,000	30	85	
Z10	26. 8. 49	100	-	100	-
Z44	14. 2. 50	300	10	72	-

Protein-uria	Tubular casts	Apathy	Appetite	Thirst	Temperature °F	Pulse
++	+	++	-	++		Weak
		++	+	++		
±		++	-	++		
+	+	-	+	+		
+	-	+	+	++		Hard
++	+					
		++	-	++		Weak
400	+					
1,000	-					
++	+		Emesis	++		Hard
++	+					
+++	-					
++	++	++	-	++		
300	+					
500	-					
400	-					
500	-					
200	-	+++	-	++		Hard
		Fractured skull				
+	+	++	±	++		
++	+	++	-	++		

Case No.	Date	L. C.	L. I.	Blood Urea	Lepto-spiruria
296	15.6.48	100	-	500	-
A243	19.9.50	100	10	89	
A289	13.12.50	300	100	81.6	-
	29.11.51	300	30	49	-
A292	23.10.50			32.4	-
	30.10.50			42	-
	2.4.51	30	10	57.8	-
A299	21.2.51	30	10	104	-
A328	9.11.50	300	30	64	-
	7.12.50	100	10	99.2	-
A526	13.3.51			107.2	
	16.3.51	300	100	104.5	
A648	5.6.51	1,000	100	91	-
	25.7.51			66	-
	11.10.51	30	-	98	-
	23.11.51	300	30	111	-
A657	12.6.51	100	10	53	-
	29.6.51	100	10	39	-
A668	18.6.51	30	10	71	-
A689	1.7.51	1,000	100	177.5	
A699	13.7.51	30	10	127	-
A743	8.8.51			64	-
	21.8.51	300	10	94.6	-
A745	9.8.51	1,000	100	132	-

Proteinuria	Tubular casts	Apathy	Appetite	Thirst	Temperature ° F	Pulse
		++	Emesis ±	++		Hard 100
+	-	-	++	+		Hard 110
50	-					
+	+	±	++	++		Hard 120
±	+	-	++	-		Hard
400	+					
120	-					
±	++	-	++	-		
±	+					
70	+	+	+	++		
200	-	+	+	++		
200	-					
160	-	+	++	++	101.8	
150	-	±	±	++		Hard 120
200	+	-	++	+++		Hard
200	++					
600	+++	-	++	++		
		++	-	++		
100	-	+	-	++		
150	+	Hysteria	++	++	101.6	Hard 120
200		-	++	++	102.4	
800	++	++	+	++		

Appendix 7

Total and differential leucocyte counts.

Primary and secondary renal stages.

TABLE 23

Total and Differential Leucocyte Counts

of 15 Cases in the Mild Primary Renal Stage.

Case	Total per c. mm.	Non-Lob. Neutrophil	Lob. Neutrophil	Basophil	Eosinophil	Lymphocyte	Monocyte
109	16,000	22	56	0	1	17	4
127	16,200	19	52	0	8	21	0
248	11,000	19	63	0	5	10	3
340	11,000	11	57	0	6	23	3
407	10,000	19	58	0	3	17	3
450	12,200	15	71	0	3	10	1
452	54,600	42	53	0	1	4	0
545	11,600	16	55	0	11	16	2
550	19,000	34	56	0	5	5	0
A619	9,600	28	40	0	6	17	1
A715	24,600	28	55	0	1	14	2
A795	20,800	4	85	0	0	11	0
A814	12,400	32	41	0	8	10	0
31X	11,000	40	53	0	2	5	0
35X	27,000	42	39	0	0	17	2

TABLE 24

Total and Differential Leucocyte Counts

of 30 Cases in the Severe Primary Renal Stage.

Case	Total per c.mm.	Non-Lob. Neutrophil	Lob. Neutrophil	Basophil	Eosinophil	Lymphocyte	Monocyte
115	4,800	23	58	0	4	15	0
470	22,600	22	63	0	3	11	1
513	49,600	38	59	0	0	3	0
514	18,800	24	41	0	21	14	0
520	9,000	55	21	0	8	16	0
544	11,200	37	54	0	3	6	0
552	10,000	16	59	0	8	16	1
560	18,200	18	64	0	4	9	5
A257	15,200	21	53	0	2	11	3
A289	15,800	18	45	0	5	27	5
A485	15,800	9	61	0	15	15	0
A549	33,000	46	35	0	6	12	1
A627	17,000	7	53	0	16	20	1
A720	24,000	18	58	0	0	8	9
A789	29,600	15	69	0	8	8	0
A793	18,400	12	77	0	5	5	1
A801	54,600	27	61	0	2	10	0
A848	15,000	19	56	0	7	15	0
A852	17,200	21	72	0	4	2	1
A874	18,000	32	64	0	0	4	0
6X	8,000	4	73	0	10	12	1
11X	14,400	11	63	0	5	19	2

TABLE 25

Total and Differential Leucocyte Counts

of 21 Cases in the Most Severe Primary Renal Stage.

Case	Total per c. mm.	Non-lob. Neutro-phil	Lob. Neutro-phil	Baso-phil	Eosino-phil	Lympho-cyte	Mono-cyte
52	10,800	10	64	0	4	20	2
143	29,000	18	65	0	4	8	5
150	15,600	16	64	0	2	15	3
152	11,600	11	53	0	4	32	0
318	20,000	11	70	0	5	12	2
324	7,000	10	58	0	4	25	3
384	10,000	11	33	0	19	32	5
443	23,200	26	70	0	1	1	2
467	11,000	8	60	0	1	29	2
499	20,200	28	55	0	2	14	1
501	10,800	12	56	0	3	24	5
507	55,600	66	25	0	0	8	1
515	20,400	18	62	0	8	7	5
553	15,200	9	63	0	8	20	0
559	13,000	17	82	0	0	1	0
563	47,600	32	67	0	0	1	0
564	17,700	16	65	0	2	17	0
565	10,200	34	36	0	2	3	0
574	29,200	21	74	0	0	1	4
A51	15,200	32	55	0	0	10	3
A307	21,800	22	56	0	3	5	14

TABLE 26

Total and Differential Leucocyte Counts

of 18 cases in the Secondary Renal Stage Without Uraemia.

Case	Total per c. mm.	Non-Lob. Neutrophil	Lob. Neutrophil	Basophil	Eosinophil	Lymphocyte	Monocyte
101	13,400	18	49	0	7	23	3
102	19,400	20	74	0	0	5	1
168	11,000	14	56	0	5	21	4
193	16,600	22	62	0	0	13	3
207	8,200	6	51	0	16	25	2
250	8,200	6	55	0	2	32	5
257	8,200	15	55	4	3	18	5
301	17,000	24	56	0	7	4	0
304	10,600	13	51	0	1	30	5
461	33,600	26	65	0	0	7	2
581	10,400	36	50	0	1	11	2
A12	12,000	14	71	0	5	6	4
A26	3,600	37	36	0	0	26	1
A50	8,600	26	54	0	1	18	1
A221	16,000	19	78	0	0	2	1
A421	14,600	55	43	0	0	2	0
A474	14,600	42	55	0	0	3	0
A849	20,100	55	32	0	2	9	1

TABLE 27

Total and Differential Leucocyte Counts

of 25 Cases in the Secondary Renal Stage with Uraemia.

Case	Total per c. mm.	Non-Lob. Neutrophil	Lob. Neutrophil	Basophil	Eosinophil	Lymphocyte	Monocyte
110	16,600	31	59	0	0	7	3
142	13,600	31	66	0	0	2	1
155	6,800	12	72	0	2	12	2
159	18,000	29	60	0	0	10	1
162	10,000	18	66	0	0	15	1
163	13,600	26	70	0	0	0	4
168	14,400	18	69	0	0	12	1
172	9,800	21	55	0	7	16	1
175	13,200	11	32	0	0	48	9
185	6,800	12	55	0	0	27	2
195	4,000	40	30	0	0	27	3
226	14,600	26	63	0	0	4	7
247	10,200	13	55	0	13	16	3
300	6,400	21	57	0	0	16	6
390	12,600	25	66	1	3	4	1
471	7,000	7	73	0	6	12	2
510	21,400	56	31	0	3	10	0
567	6,200	21	53	0	10	9	0
573	34,200	52	46	0	0	2	0
A33	23,400	33	62	0	0	5	0
A70	5,200	23	64	0	2	8	3
A80	46,600	28	69	0	0	3	0
A260	13,600	38	52	0	0	8	2
A270	9,400	19	68	0	1	8	0
A340	15,400	24	72	0	0	4	0

Appendix 8

Erythrocyte and haemoglobin estimations.

Primary and secondary renal stages.

TABLE 28

Haemoglobin and Erythrocyte Estimations

of 13 Cases in the Mild Primary Renal Stage.

Case	P. C. V. %	Haemoglobin gm./100 ml.	R. B. C. 10^3 per c. mm.	M. C. H. u. u. g.	M. C. H. C. %	M. C. V. c. u.
340	53	16	6,200	25.8	30.2	85.5
407	55.5	17.5	7,000	25	31.6	79.2
545	50	14	6,000	23.3	28	83.3
A619	39	12.8	5,350	24.1	33	72
109		11.6	5,150	22.7		
127		15.7	7,100	22.1		
248		14.3	6,500	22		
450		16	7,500	21.3		
452		15.4				
550		12.3	5,250	23.8		
A814		16	7,450	21.6		
31X		12.2	4,800	25.3		
35X		15.1	6,350	23.9		

TABLE 29

Haemoglobin and Erythrocyte Estimations

of 25 Cases in the Severe Primary Renal Stage.

Case	P. C. V. %	Haemoglobin gm./100 ml.	R. B. C. 10^3 per c. mm.	M. C. H. u. u. g.	M. C. H. C. %	M. C. V. c. u.
104		16.5	6,150	27		
105		14.4	7,400	19.3		
110		11.8	5,900	20		
115		16.1	7,400	21.6		
129		16.1	7,300	22		
151		9.8	4,200	23.2		
179	58	17.9	7,150	25.2	30.8	83
204	54	16	5,200	30.7	29.4	104
212	52	15.4	6,800	22.6	29.6	76.4
276	51.5	15.5	5,950	26.2	30.1	86.5
282		12.0	4,550	26.6		
470		13.9	6,300	22		
513		17.1	8,800	19.4		
514		7.7	3,500	22		
520	53	16.8	5,800	28.9	32	91
552	58	17.1	7,750	22.2	30	75
560		14	6,050	23.3		
A8		15.4	7,500	20.5		
A289	56	15.1	6,050	25.2	27	92
A485		16.7	6,700	24.8		
A627	36	11.5	4,750	24.4	32	75
A848		13.3	5,650	23.7		
A883	39.2	12.5	3,950	32	32	99
6X		10.2	4,440	23.1		
11X	54	16.5	5,450	30.6	31	99

TABLE 30

Haemoglobin and Erythrocyte Estimations

of 20 Cases in the Most Severe Primary Renal Stage.

Case	P. C. V. %	Haemoglobin gm./100 ml.	R. B. C. 10^3 per c. mm.	M. C. H. u. u. g.	M. C. H. C. %	M. C. V. c. u.
52	57.5	17.2	7,000	24.5	29.9	82.0
143		9.1	4,550	20.2		
150		12.6	6,000	21		
152		10.5	4,100	25.7		
318	51.1	17.4	5,550	31.6	34	92
324	49	15.1	5,100	29.6	30.8	96
384		8.4	3,850	22.1		
443		10.9	5,600	19.2		
467		8.5	3,600	23.6		
499		16.7	6,550	26.6		
507		11.8	4,200	28		
515		7.0	3,450	20.5		
553	56.5	15.4	5,500	28	27.2	102.7
559		14.4	5,500	26.1		
563		16.8	6,050	28		
564	22.9	7.6	3,050	25.3	33.2	75
565	51	14.6	5,750	25.6	28.6	88.7
574	38.5	11.9	5,350	22.4	30.9	72
A51		15.7	6,200	25.3		
A307	49	17.22	9,100	18.9	35	54

TABLE 31

Haemoglobin and Erythrocyte Estimations

of 18 Cases in the Secondary Renal Stage Without Uraemia.

Case	P. C. V. %	Haemoglobin gm./100 ml.	R. B. C. 10^3 per c. mm.	M. C. H. u. u. g.	M. C. H. C. %	M. C. V. c. u.
101		13.7	6,400	21.4		
102		15.4	6,400	24		
166		11.9	5,800	20.5		
168	54.5	16.8	6,250	27	30.8	87
174		14.1	7,100	19.8		
193		13.3	6,350	21.1		
207	57	16.8	6,950	24.3	29.5	82
250	55	16.7	5,750	29.2	30.4	95.6
257	53	16.4	4,750	34.9	31	111.5
301	54	16.7	5,900	28.2	30.8	91.5
304		11.5	4,800	23.5		
461		11.2	4,600	24.3		
581		12.2	4,900	24.8		
A12		13.8	5,700	24.2		
A50		17.1	6,250	27.5		
A221		18.5	6,800	27.2		
A421		12.9	4,950	26.3		
A474	37	11.5	4,000	28.7		

TABLE 32

Haemoglobin and Erythrocyte Estimations of 28 Cases in the Secondary Renal Stage With Uraemia.

Case	P. C. V. %	Haemoglobin gm./100 ml.	R. B. C. 10^3 per c. mm.	M. C. H. u. u. g.	M. C. H. C. %	M. C. V. c. u.
110		14.3	6,400	22.3		
142		15.4	7,250	21.3		
147		10.5	4,350	24.4		
155		11.2	6,000	18.6		
159		11.2	5,250	20.3		
162		6.3	2,800	22.5		
163		16.8	7,400	22.7		
165		9.9	3,500	28.2		
168		18.2	7,150	25.6		
172		11.5	5,700	20.1		
175		13.7	6,300	21.7		
177		8.4	3,950	21.6		
185		12.3	6,600	18.5		
195		11.2	4,550	24.9		
226		14.7	7,100	20.7		
247	38	11.9	4,050	29.7	13.3	93.7
300		5.0	2,200	22.7		
364		3.5	700	50		
390		8.5	3,050	28.3		
510		11.9	4,800	24.7		
567	50	15	5,800	25.6		
573	24.5	9.1	3,000	30.3		
A70		8.3	2,900	28.6		

Case	P. C. V. %	Haemoglobin gm./100 ml.	R. B. C. 10^3 per c. mm.	M. C. H. u. u. g.	M. C. H. C. %	M. C. V. c. u.
A80		18.9	9,000	21		
A260		9.2	3,850	24.2		
A270		15.4	6,150	25.2		
A340		4.8	1,350	36.7		
A585		12.8	4,150	31.2		