THE EFFECT OF NEPHRITIS ON OTHER BODY SYSTEMS OF THE CANINE

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INTRODUCTION

In general, diseases of the kidney can be classified into three distinct categories: degenerative (nephrosis), inflammatory (nephritis) and vascular (arteriosclerotic). The parenchymatous elements, comprising the glomeruli and tubules; the vascular elements, involving the arterioles and capillaries; and the interstitial elements, consisting of the stroma, can be involved separately or jointly. The most common renal inflammatory disease in man is glomerulonephritis, while interstitial nephritis is of minor significance. The terms hemorrhagic and parenchymatous nephritis often are used synonymously with glomerulonephritis. In the dog, interstitial nephritis is of paramount importance, whereas glomerulonephritis is not commonly found. Primary vascular lesions of the kidney are extremely rare in dogs. Hutyra and Marek mention acute and chronic nephritis, the former divided into parenchymatous and diffuse types, and the latter into the diffuse (parenchymatous, glomerulonephritis) and indurative (interstitial) forms.

Jacob (1924) believes that epithelial or tubular nephrosis and nephrocirrhosis occur most commonly. Müller and Glass (1926) classify nephritis as the acute and chronic forms. The chronic form is subdivided into the parenchymatous and interstitial types, and while no classification of the acute form is given, it is apparent from the pathological description, that the parenchymatous type is meant. Brumley (1931) divides acute nephritis into three groups, namely: parenchymatous, hemorrhagic parenchymatous, and diffuse, while the chronic form was classified the same as by Müller and Glass. McNider (1916) classified the renal lesions observed in forty-two naturally nephropathic dogs as chronic glomerulonephrits. However, it is

difficult to reconcile such a pathological diagnosis with the type of renal changes described. The lesions discussed would appear to be primarily interstitial.

Capable and experienced pathologists are universally in agreement that interstitial nephritis is the most common and important inflammatory renal disease in dogs, while glomerulonephritis rarely occurs.

To the physician, nephritis is a disease of considerable frequency and importance. To the veterinarian, nephritis in dogs is probably of equal, if not greater, significance. A perusal of the literature, both medical and veterinary, indicates that Bright's disease has been well studied, while interstitial nephritis, with few exceptions, has been only superficially examined. Nephritis is the most important and frequent among the affections observed in the urinary tract of the canine species. The importance of this condition lies in its frequent occurrence and its deleterious consequences on other body systems of the dog.

Historically, Hippocrates, the father of medicine, is credited to have observed nephritis in man for he commented on the bubbles in urine and correlated it with kidney disease. Rufus (100 A.D.); Aetius of Amida (502-575); Paul of Aegina (625-690); Rhazes (850-923); Avicenna (980-1037); and Williams of Saliceto (1269-1274) were all acquainted with chronic nephritis and described the anatomical changes that occurred. Bellini (1643-1704) stressed the importance of physical examination of urine in kidney disease.

Boehaave (1669-1738) included the chemistry of urine in his study of kidney disease. Fredrick Dekker (1648-1720) was the first to demonstrate albumin in urine by boiling it with a drop of acetic acid. Van Baptista

(1577-1644) made the first gravimetric examination of urine. In 1811 Charles read a paper in which he reported finding albumin in the urine in 78 cases of dropsy. Richard Bright (1789-1858) associated albuminuria with sclerosis and dropsy and made detailed clinical and post-mortem examinations of patients with nephritis. Henle (1841) and (1847) studied the histological details of kidneys.

The principal renal inflammatory disease of the dog is interstitial nephritis, which may be acute, subacute or chronic (Hoare, 1910; Mcfeydeyan, 1929; Bloom, 1939; Milks, 1944; Kirk, 1948; and Leonard, et al., 1953). Interstitial nephritis was first described by Davis (1908) and subsequently Joest (1924); Nieberle and Cohrs (1931) reported on the frequent occurrence of this condition.

It is interesting to note that contrary to what other earlier and later authors have remarked, Saunders (1915) and Müller and Glass (1923) observed that diseases of the kidneys in the dog were relatively unimportant. On the other hand, Bloom (1939, 1954) mentioned that some degree of interstitial nephritis occurs in practically all dogs over 8 years of age and in approximately 50 percent of dogs of all ages in routine necropsies. Leonard, et al. (1953) observed that "diseases affecting the urinary system in the dog, particularly those connected with kidney disturbances are among the most common ailments of dogs, especially in the older age group. Most old dogs will show some kidney damage in the normal course of living." These views were shared by Hoare (1911); Dayton (1914), who found only one dog among 21 with normal kidneys; McNider (1916); Wright (1932); Institute of Animal Pathology (1940); Milks (1944); Frischbier (1949); Steel (1952); Runnels (1954); Smith (1955); and Zontine (1957).

Smith and Jones (1954) observed that "there are as many classifications of nephritis as there are writers on the subject." The etiological classification is divided into those due to infectious agents and those due to non-infectious agents. Among the infectious agents, bacteria are the most important. Organisms found associated with nephritis include - E. coli, Proteus vulgaris, streptococci, pseudomonas, Aerobactor aerogenes (Haines, 1945; Rollag, 1947; Bloom, 1954; Featherston, 1958; Mosier and Coles, 1958; and Coles and Mosier, 1959). Bacterial nephritis in addition to reducing functional renal tissue, may be conducive to the production of urolithiasis (Smith and Jones, 1954; Brodey, 1954). Nephritis, especially chronic nephritis, results in scarring. When the functional tissue is reduced, the vital functions including excretion of waste products, reabsorption of vital constituents, and formation of ammonia are seriously hampered. Scarring may result in hypertension in dogs (Hartman, et al., 1927). An imbalance in calcium and phosphorus excretion may give rise to hyperparathyroidism and attendant changes in the skeleton (Brown and Gainsburgh, 1939). Thus it is evident how vital the kidney is, that how the importance of the diseases of this organ cannot be overestimated and that one cannot overemphasize the necessity of diagnosis of nephropathies in their early stages. Unfortunately, our knowledge as to the genesis of nephritis or of the methods of diagnosis of such a condition is limited and fragmentary. Various tests have been devised to measure the function of different components of the nephron and to pinpoint the locus of damage in order that appropriate therapeutic measures could be taken. Such tests, though used and tried in man in various diseases, have had relatively limited trials in veterinary medicine.

A statistical approach to the study of any disease is of paramount importance to the clinician. Veterinary pathologists are almost in universal accord that renal inflammatory lesions occur with great frequency in the dog. Joest cites the following references: Porcher (1895) and Leblanc (1899), particularly emphasized the frequency of shrunken kidneys. Davis (1908), in autopsies of 145 dogs at the Bern Veterinary High School, found kidney changes in 27 percent. Siebel (1910) saw macroscopic kidney changes in 7 percent of the dog autopsies at the Berlin school. Of 250 dogs that the workers in the Stockholm school examined, not less than one-third showed macroscopic kidney changes, and microscopically only one-fourth were normal. This research was confirmed by Pfeiffer (1912), who found that it was difficult to obtain a completely normal kidney from the dog. Henschen reported the frequency of macroscopic inflammatory renal changes to be from 40 to 50 percent in pointers and Saint Bernards, 35 to 40 percent in terriers and Great Danes, and 21 to 32 percent in dogs of the setter, spitz, beagle, and dachshund breeds.

THE EFFECT OF NEPHRITIS ON:

Body as a Whole

The onset of acute interstitial nephritis is sudden and the patient is depressed. The appetite is poor or entirely lacking, but thirst is increased (polydipsia) and vomiting is frequent. Temperature elevation is moderate to high, depending on the stage at which the patient is seen. In severe cases the back is arched, the gait is stiff, and there is pain on palpation over the lumber and upper abdominal regions. Urine is usually scant. The pulse

is full and bounding, the mucous membranes are congested, and the coat and skin show evidence of dehydration.

The early stage of chronic interstitial nephritis is marked by increased thirst and sometimes increased hunger and emaciation. The dog may have vague digestive upsets with irregular episodes of vomiting and dyspepsia. The eyes have an anxious appearance, the coat is rough and the animal is dehydrated. There is an unthrifty and sometimes eczematous appearance to the skin. In later stages, diarrhea may be pronounced. The patient voids large amounts of pale, watery urine (polyuria) that has a low specific gravity.

Especially prominent signs of uremia are vomiting, low-normal to subnormal temperature, congestion of the conjunctiva, and altered attitude. The neurological symptoms usually range from depression, weakness, and drowsiness to a comatose state, although muscular twitchings of a fibrillary type sometimes occur. There is a fetid oral odor. Necrotic stomatitis or glossitis may leave well-defined ulcers in the mucosa. There may be a brownish discoloration of the tongue and teeth. Other symptoms sometimes observed are constipation or diarrhea (which may be bloody), secondary hypoplastic anemia, emaciation, and possibly eczema.

Dogs with a significant amount of chronic interstitial nephritis have attacks of uremia, which may be intermittent and often follow periods of excessive physical exercise or the consumption of excessive amounts of food that is high in protein. In these two circumstances, the kidney is presented with the task of eliminating an unusually large amount of protein break-down products. Whereas, normal kidneys have a sufficient overload capacity to take care of this need, the kidneys in chronic interstitial

nephritis may be unable to do so, and uremia results.

Urea was early implicated as the cause of uremia by Christison in 1829. The recent demonstration (Grollman and Grollman, 1959) that bilaterally nephrectomized dogs dialyzed by intermittent peritoneal lavage against high concentrations of urea developed weakness, anorexia, vomiting, hemorrhagic diarrhea, and coma after several days, despite a normal electrolyte composition of plasma, lends weight to this hypothesis.

Phenols, present in high concentrations in blood and spinal fluid, have been held responsible for uremic symptoms (Becher, 1933). Although phenol intoxication resembles some of the features of uremia (Mason et al., 1937), the evidence in favor of this hypothesis is tenuous.

In 1915 Foster reported the isolation of an organic base, apparently guanidine (Harrison et al., 1937), from the blood of uremic patients which, when injected into the peritoneal cavity of guinea pigs, caused rapid respiration, convulsions, and ultimately death.

Harrison and his co-workers (1936, 1937) and subsequently others (Andes et al., 1937) demonstrated increased concentrations of a guanidine-like material in blood and spinal fluid of experimentally uremic dogs and clinically uremic patients. Guanidine, injected into experimental animals, produces muscle twitching, hyperexcitability, paresis, and convulsions, as well as hemorrhagic bowel lesions. Experimentally, therefore, guanidine can produce some of the features of the uremic syndrome.

In uremia, two groups of clinical symptoms are present. First, symptoms referable to deranged renal excretory and regulatory function, characteristic of renal failure, are prominent. Secondarily, a unique constellation of gastrointestinal, cardiovascular and neuromuscular disturbances develops

which are independent of, though often similar to, concomitant disturbances caused by electrolyte abnormalities, hypertension, and hematologic disorders such as anemia.

Digestive System

The occurrence of gastrointestinal lesions in uremia has long been recognized, but the comprehensive study of a large series of cases was not reported until the work of Jaffe and Laing appeared in 1934.

Anorexia, nausea and vomiting are common in uremia, and occasionally constitute the first symptoms of renal disease.

Though patients in uremia may have little or no free hydrochloric acid in gastric juice, this is not necessarily a result of a failure in hydrochloric acid production. Rather, it develops because of the increased formation in gastric juice of ammonia which then neutralizes gastric acidity. Accelerated ammonia production, in turn, has been attributed to the high levels of blood urea which elevate the concentration of urea in gastric juices where it is hydrolyzed, under the influence of urease, to ammonia (Lieber and Lefevre, 1959). The hydrolysis of urea to ammonia is probably responsible for the ammoniacal taste and odor in uremia.

Although constipation is more common, diarrhea, often bloody, tends to appear in the later stages of renal failure. It causes severe depletion in extracellular volume as well as potassium deficiency. Anemia is often greatly aggravated. It should be borne in mind that bleeding originates anywhere in the gastrointestinal tract. The colon, stomach and duodenum are frequent sites. Bleeding usually occurs from ulcers of the mucosa, although at times only ill-defined mucosal hemorrhages are observed.

Mucosal ulcerations also occur in the mouth. The ulcers may be small and punctate on the gums, but can attain large size particularly on the lips and at the corners of the mouth. Salivation may be increased as ulcers develop.

Marked abdominal pain, sometimes with generalized tenderness, develops especially in those patients with severe vomiting and diarrhea. The pain may be associated with ulcerative lesions.

The cause of the gastrointestinal disorders is not clear. Anorexia, nausea, and vomiting have been attributed to central nervous system disturbances. Ulcerative lesions may be responsible for diarrhea and perhaps to some extent vomiting as well. They have also been thought to result from the high ammonia content brought about by the action of bacterial flora on urea which is excreted vicariously by the digestive tract in uremia.

Streicher in 1928 was able to produce marked gastroenteritis in dogs with one or both kidneys functioning by the intravenous administration of 10 percent and 20 percent urea solutions, 200 cc. daily, given slowly by drip method for three days. A syndrome resembling uremia developed progressively during the urea administration, terminating with convulsions, bloody diarrhea, coma and death after 500 to 600 cc. of urea solution had been injected. Autopsies performed on all animals revealed injection and hyperemia of the entire gastrointestinal tract, but no necrosis or ulceration was described. Histologic examination of tissues was reported as revealing gastrointestinal inflammation. Photographic illustrations of the enteritis, which was described as congestion of the mucosa, was later interpreted by Jaffe as appearing hemorrhagic rather than congested.

Bollmann and Mann in 1927 studied the nitrogenous constituent of the blood in dogs following transplantation of ureters into different levels of the intestine, and observed marked elevation in blood urea without an increase in other nitrogenous substances in those animals having no evidence of uremia until the terminal one to two days, preceding which the blood urea levels decreased considerably. Necropsy of the dogs revealed hemorrhagic lesions in the stomach similar to those found in cases of uremia. No pseudomembranous or ulcerative lesions were found. In a discussion of the work Hench stated that these experiments afforded additional evidence that urea is a practically nontoxic substance, and expressed the opinion that, in the presence of such an intense "local uremia" as should be existent in the intestinal mucosa under the conditions of these experiments, one would expect the development of lesions in the gastrointestinal tract sooner than anywhere else.

Cardiovascular System

Generally in uremia caused by nephritis, the heart is subjected to various adverse influences. When uremia supervenes in chronic renal disease, hypertension and left ventricular hypertrophy usually are already present and show the strain to which the left ventricle is subjected. In acute renal disease, hypertension and uremia may evolve concomitantly, or either may precede the other. The heart may also be affected by anemia, coronary disease, myocarditis correlated with infection producing or complicating the renal disease and myocarditis subjacent to uremic pericarditis.

Pericarditis occurs in the terminal stages, indicating almost invariably that the dog will soon expire. This uremic lesion is common in man and

occasionally in dogs terminating the course of chronic nephritis (Smith and Jones). Uremic pericarditis may produce the usual pericarditic changes in the tracing.

The pathogenesis of uremic pericarditis has been much discussed. The suggestion has been ventured that dehydration may produce pericardial cell damage by diminishing the fluid needed for lubrication of the constantly moving surfaces. But this explanation is difficult to reconcile with the frequent development of pericardial effusion.

In a majority of uremic cases heart failure sooner or later supervenes. Paroxysms of cardiac asthma and pulmonary edema due to left ventricular failure are common. In most uremic cases, congestive heart failure ultimately develops, with passive engorgement of both the greater and lesser circulations. Pulmonary edema is usually a terminal or terminating manifestation.

The heart failure of uremia is probably most often due to a combination of the factors listed above, as well as to the effect on myocardial function of the changes in the chemical composition of the blood resulting from renal insufficiency.

In the many studies undertaken during the past two decades with view to the better understanding of the pathogenesis of hypertension in man, the dog has been widely used as the experimental animal. Goldblatt and his collaborators (Goldblatt, Lynch, Hanzal and Summerville, 1934; Goldblatt, 1937, 1938, 1946; Goldblatt, Gross and Hanzal, 1937), Winternitz Nylon, Waters and Katzenstein, 1939, 1940) and Muirhead, Vanatta and Grollman (1949) have all studied various aspects of induced hypertension, while Holman (1941, 1943, 1947), Holman and Hewitt (1942), Holman and Swanton (1946) and McCormick and Holman (1949) have directed attention to the necrotising

cardiovascular changes which frequently accompany experimental acute renal insufficiency in dogs. Comparatively little attention, however, has been given to the structural alterations in the cardiovascular system that arise in the course of the naturally occurring nephritides of dogs.

H. Platt (1952) studied the effects of acute and chronic nephritis upon the structure of the cardiovascular system in 8 dogs with acute and 24 with chronic nephritis. The changes observed were of two main types: (1) those due to hypertension, seen only in dogs with chronic nephritis; (2) necrotising lesions in the heart and great vessels, mainly in dogs with acute nephritis, and scars at these same sites in dogs with chronic nephritis.

Cardiac hypertrophy was present in 6 out of 16 dogs with chronic nephritis and the LV:RV ratio was higher in chronic nephritis cases generally than in normal dogs.

Fibrinoid lesions occurred in the glomeruli, and sometimes in the renal and other arterioles as well, in 15 out of 22 dogs with chronic nephritis. These lesions were not found with acute nephritis.

Acute necrotising lesions were found in 5 out of 8 cases of acute nephritis; the left auricle, aorta and pulmonary artery were the principal affected sites. These lesions were found in only 1 out of 24 dogs with chronic nephritis. Scars were present at these sites in 8 out of the 24 chronic nephritic animals.

H. Platt concluded that hypertension is an important feature of chronic nephritis in the dog, and that the necrotising cardiovascular lesions seen in acute nephritis are probably not of hypertensive origin, but are identical with those occurring in experimental renal failure in the dog. In dogs surviving the acute stage of nephritis, the necrotising lesions undergo

healing and scarring. He could not explain the cause for these necrotic lesions.

Chrug and Lehr (1954) described lesions in the smooth muscle of the aorta, gastrointestinal tract and the myocardium in rats in which severe nephropathy was produced by the injection of poorly soluble sulfonamide compounds. The muscle fibers underwent hydropic degeneration, followed by fragmentation. An intense inflammatory reaction occurred, the exudate consisting of polymorphs. Calcium was deposited where degeneration occurred.

Sporri, et al. (1961) studied blood pressure in 14 dogs with chronic nephritis. In those without uremia, systolic and diastolic pressure was normal. In those with uremia, systolic pressure was high but within normal limits; diastolic pressure was up to 20 mm. mercury above normal. Blood pressure in dogs with kidney diseases was considered to be less conclusive than in human patients and it appeared unjustified to attribute the cardiac hypertrophy, present in chronic nephritis, solely to increased blood pressure.

Wood and White (1925) reported that in certain cases of uremia and severe nephritis with an increased blood nitrogen there is a toxic effect acting in some respects like digitalis on the heart muscle. It may produce abnormal electrocardiogram changes in T wave of Lead II, less often abnormal rhythm, and rarely an increase in the auriculo-ventricular conduction interval or in the duration of the QRS complex.

Pathological, metabolic and organic changes which cause an alteration in the electrolyte levels in the serum will frequently result in the presentation of an abnormal electrocardiogram. The ions usually affected by these changes are potassium, sodium, and the chlorides. These ions have as one of their functions the regulation of the heart beat and the heart rate.

The heart is bathed in a solution of these ions (Best and Taylor, Birch and Winsor) and they play a part in the transmission of the waves involved in depolarization and repolarization to the electrodes of the electrocardiogram. Any change in their concentration may manifest itself by a corresponding change being recorded on the tracing.

In nephritis or nephrosis, and especially in uremia, the serum-electrolyte balance is altered, due to abnormal filtration by the glomeruli or imparied function of the tubules. The electrocardiogram changes seen are usually produced by a potassemia (hyperkalemia). Potassium retention or a rise of the potassium level in the serum usually occurs along with an upset in the sodium and/or chloride levels in the serum during the course of the nephritis, nephrosis, or uremia.

One of the functions of potassium is its association with acetyl choline at the myoneural junction; the presence of potassium is necessary for impulse conduction and muscular contraction of the heart.

The earliest report of potassium poisoning in nephritis is that by W. G. Smillie in 1915. In potassemia, the conduction of the impulse is depressed so that some degree of bradycardia, or slowing of the heart rate, may be evidenced. The T waves are of long duration and a resulting increase in the Q-T interval occurs. An increase in the Q-T interval associated with clinical evidence is indicative of electrolyte imbalance with potassium retention. The Q-T interval in well-developed cases of renal damage is usually over 0.22 seconds (Soave, 1954). Lannek (1949), in his study of electrocardiograms in dogs with nephritis, found Q-T intervals of over 0.20 seconds.

Finch and Marchand (1943) observed the following symptoms in experimental poisoning induced by severe acute nephritis: (1) an acute uremia with oliguria; (2) recurrent nausea and retching; (3) episodes of bradycardia unaccompanied by symptoms of cardiac failure; (4) electrocardiographic changes including elevated T waves, absent P waves, intraventricular block, and terminal irregularity of rhythm; (5) arrest of the heart in diastole prior to the cessation of respiration.

Winkler, Hoff and Smith (1938, 1942) showed that in dogs a slow increase of the serum potassium from normal levels of 4 to 5 m. eq./l., to 14 or 16 was accompanied by a progressive elevation of the T waves, depression of the S-T segment, intraventricular block, loss of P waves, and finally cardiac arrest.

Subsequent studies demonstrated spontaneous potassium poisoning regularly in surgically anuric dogs (Winkler, Hoff and Smith, 1941) and occasionally in adrenalectomized dogs as suggested by the work of Nicholson and Soffer in 1935.

Wood and Moe (1942) found in heart-lung preparations from dogs that atrial and ventricular arrest occurred at average plasma potassium concentration of 8.5 and 9.5 m. eq./l., respectively.

Nervous System

The first nervous symptoms of uremia caused by nephritis are often those of muscular weakness and torpor (Fishberg, 1954).

Symptoms such as headache are not easily evaluated in animals; nervous hyperirritability, including convulsions in dogs, is usually ascribed to the lowering of calcium, although the status of the magnesium level would bear investigation in this regard. The cerebral edema which is common in humans

seldom accompanies uremia in the domestic animals (Smith and Jones, 1958).

The neurological symptoms usually range from depression, weakness, and drowsiness to a comatose state, although muscular twitchings of a fibrillary type sometimes occur (Canine Medicine, 1962).

Muscular twitching and, far less frequently, convulsions, are thought by some clinicians to be caused by a decrease in the ionized calcium of blood due to renal retention of phosphate. But the relation of symptoms to plasma calcium is tenuous, and it has been suggested that the defect in calcium is in the nervous system itself. Observations in nephrectomized dogs indicate that the onset of twitching is more closely related to increased inorganic phosphate in cerebrospinal fluid than to the increase in plasma. The ionized calcium of the cerebrospinal fluid is often significantly lowered (3 mg. per 100 ml. as compared to normal 4.3 with a rise in inorganic phosphate from 1.3 to 2.7 mg. per 100 ml.).

Musculoskeletal System

In the dog, renal failure and uremia usually results from chronic nephritis. In such patients the urine volume is usually large until shortly before death. Hyperkalemia is not so significant as in acute renal failure. Indeed, the mechanism of potassium excretion, inadequately balanced by concurrent hydrogen ion formation, may be so active as to cause potassium clearance to rise to levels well above filtration rate so that there ensues an actual depletion of plasma potassium with resultant weakness and paresis of skeletal muscles. Such cases, however, are less common than those in which, as in acute renal failure, terminal potassium intoxication results from failure of urine flow (Sodeman, 1963).

Muscular twitching and, far less usually, convulsions, are thought by some clinicians to be caused by a decrease in the ionized calcium of blood due to renal retention of phosphate (Smith and Jones, 1958). Intravenous administration of calcium tends to relieve twitching, and oral dosage with aluminium hydroxide tends to relieve the defect in ionizable calcium and some of the acidosis by causing fecal excretion of insoluble aluminium phosphate (Sodeman, 1963).

The defect in calcium metabolism extends much further and reaches earlier into the course of renal failure. The tendency toward depression of ionized calcium acts as a stimulus for parathyroid hyperplasia, which is manifested functionally and structurally. Functionally, it results in decalcification which leads to the disease entity known as renal osteodystrophy (rubber jaw), which is primarily a nephritic condition with bone lesions, particularly of the skull, appearing later (Hogg, 1948). If the condition occurs in young individuals before full growth is reached, it is called renal rickets, or renal dwarfism (Howard, 1938; Mitchell, 1930). The primary lesion responsible for the syndrome can be congenital cystic kidneys, bilateral hydronephrosis, or a long-standing severe nephritis. These lesions will result in impaired kidney function, which causes retention of phosphates in the blood stream and an elevation of the serum phosphorus level (normal level is 2-4 mg./100 cc. of blood). Some of the excess phosphates are excreted into the intestinal lumen where they combine with the available calcium, forming calcium phosphate, an insoluble precipitate. This reaction, therefore, results in a decreased calcium absorption from the intestine and thus a hypocalcemia (normal serum calcium level is 9-11 mg./100 cc. of blood). The parathyroid glands respond to

this hypocalcemia by undergoing hyperplasia and thus producing excess parathormone. Parathyroid hyperplasia has been shown experimentally by Drake, Albright and Castleman (1937). They used repeated injections of a neutral, isotonic sodium phosphate in rabbits and produced a secondary parathyroid hyperplasia. Pappenheimer and Wilens (1935) found a 50 percent weight increase of the parathyroid gland in 21 patients with nephritis. Castleman and Mallory (1937) reported on the histopathology of the parathyroid hyperplasia encountered in 29 cases of chronic renal insufficiency in man. The parathyroid hyperplasia, together with the acidosis, which often is associated with the kidney dysfunction, will cause osteomalacia by mobilization of calcium and phosphorus from the skeleton in an effort to maintain a normal serum calcium, with formation of soft, rubbery bone (Nielsen, et al., 1954; Brodey, et al., 1961). Metastatic calcification will be present in different organs -- kidney, stomach-wall, and the large arteries (Brown and Ginsbury, 1940; Nielsen, et al., 1954; Kretzschmar, 1956).

In the dog, the clinical signs of bone resorption are confined to the jaws and the head, and thus the term "rubber jaw" is often ascribed to this disease by clinicians. Actually, there is generalized osteoporosis of all the long bones on histopathological examination. Platt (1952) states that histological evidence of bone resorption is present in most cases of chronic nephritis in the dog. It is only in a very few cases that clinical "rubber jaw" is observed (Brodey, 1954). A review of the literature (Coffin, 1953; Davis, 1936; Gratzl, 1941; Hogg, 1948; Nieberle and Cohrs, 1949; Platt, 1952) reveals that chronic nephritis associated with the above changes is not an infrequent occurrence in the dog.

Gratzl (1941) reported that 6 dogs, 5 to 13 years old, with chronic nephritis (usually following leptospirosis) showed loosening of the teeth

and softening of the jaw bone. Radiographs revealed marked osteoporosis and decalcification. Histological examination of one case showed osteodystrophia fibrosa which was hyposteotic in type (compared with hyperosteotic type in which there is an increase in size of affected bones due to deposition of osteoid tissue).

Gratzl suggested that the syndrome in the dog develops from lowering of the alkali reserve of the blood and acidosis leading to withdrawal of calcium from the bones to keep up the level of blood calcium. The osteoporosis which results is later followed by osteodystrophia fibrosa.

Dämmrich (1958) examined bones in 39 dogs with nephritis. Changes were found in the ribs and head bones, and less often in the scapula. The ribs could be bent more easily, and the compacta was more porous. The head bones to be affected first were the jaws, followed by the nasal, frontal and temporal bones. These showed porosity, increasing rarefaction and lower specific gravity. Bending of the bones (rubber jaw) occurred in seven cases. Metastatic calcification was found in the kidneys, trachea, epiglottis, endocardium, larynx and aorta in 16 of the 39 dogs. The kidneys showed macroscopically interstitial nephritis, with or without contraction. In all cases with this osteo-renal syndrome and in cases with nephritis without bone changes, the parathyroids were enlarged, 1-1/2 to 10 times. The enlargement is interpreted as parathyroid hyperplasia and hypertrophy secondary to renal change.

Hemic and Lymphatic System

The association of anemia with renal diseases has long been recognized (Hamelin, 1904; Hunter, 1888; Quinke, 1880; Widal, Abrami and Brule, 1907),

and various causes for the anemia have been suggested. A hemolytic process has been postulated by some (Hamelin, 1904; Hunter, 1888; Quinke, 1880), but denied by others (Bingold, 1933; Ceconi, 1905; Holler, 1926; Piney, 1932). Other factors which have been considered include the inhibitory effect of urinary poisons (Ceconi, 1905) and protein deficiency related to proteinuria or dietary inadequacy (Ashe, 1929; Grignani, 1921). Protein deficiency as a cause is not accepted by certain authors (Brown and Roth, 1922) and it has been pointed out that in pure lipoid nephrosis, in which proteinuria is prominent, anemia is rare unless renal insufficiency supervenes (Bannick, 1934; Wilber and Brown, 1930) as a complication. Furthermore, the diets of patients with renal diseases are not usually deficient in protein unless the patients are too ill to eat (Aubertin, 1924; Griva and Asinelli, 1932).

Brown and Roth (1922) showed that there is no relationship between hematuria and anemia. They considered defective blood formation to be an important factor in the production of anemia. It was felt that an unknown toxic substance was responsible for the deficient red cell production. Ceconi (1905), as well as others (Grignani, 1921; Nylander, 1935) considered toxic injury to the bone marrow as the basis for the anemia. Whitby and Britton (1946) stated that when there is much edema in nephritis, the anemia is often due to a disturbance of water balance, Nylander (1935) discussed selective damage to the bone marrow involving erythropoiesis, while leaving myelopoiesis intact.

Widal, Abrami and Brule (1907) examined one case and found a very active bone marrow they described as aplastic. Others (Aubertin, Yacoel, 1924 and Scarlett, 1929) also found the bone marrow replaced by fat tissue or revealing no evidence of increased marrow activity. These studies have

been criticized (Rohr, 1940; Rohr and Hafter, 1937) because of the autolysis that occurs to bone marrow tissue obtained at autopsy.

Nordenson (1938) used Arinkin's method of staining the bone marrow. An "incipient aplasia" of the erythroid tissue with a myeloid-erythroid ratio of 8 to 1 was described. Similar findings were described (Custer, 1941; Kracke, 1941) except for the presence of a normal cellular or hypercellular bone marrow. Contradictory results were reported by Giacchero and Belletti (1941) who found an increased number of normoblasts. Isaacs (1937) mentioned that the bone marrow at first suggested invasion by lymphoblastoma cells. The peripheral blood demonstrated an alteration in the red cell diameter prior to the onset of gross kidney dysfunction.

An increase in polychromatic and basophilic normoblasts with, however, a reduction of mature erythroblasts was found in 38 patients with "nephrogenic anemia" (Arinkin, 1929). Dameshek (1935) and others (DeWeerdt, 1939; Parsons and Ekolastrolberg, 1933; Young and Osgood, 1935) suggested the bone marrow revealed a distinct hypoplasia of erythropoietic tissue. The etiology of this anemia was said to bear a direct relationship to the degree of nitrogen retention, whatever the cause (Parsons and Ekolastrolberg, 1933).

Others (Läninger, 1938; Scott, 1939) noted decreased cellularity with an increased relative number of normoblasts. Reduced erythropoietic tissue without hyperactivity either erythroid or myeloid cells has been described (DeWeerdt, 1939; Loeper and Perreau, 1939; Michelazzi and DeRenzi, 1937). Vogel, Erf and Rosenthal (1937) and Falzoi (1939) noted a shift to the right in myelopoiesis of the bone marrow.

Gingold, Comsa and Roman-Crivat (1938) found the bone marrow to be unable to retain normoblasts and terminally to become aregenerative.

As the kidney lesions became progressively severe, erythropoietic aplasia became more pronounced (Faärup and Ohlsen, 1941; Nolli, 1939). Fieschi (1938) and Büchmann and Stodtmeister (1943) observed cases of chronic nephritis with uremia in which the bone marrow revealed hyperplasia of the granulocytic cells and marked reduction in the erythroblastic elements. Stem cell involvement in the bone marrow was thought to be the cause.

Leitner (1945) in 11 patients with nephrogenic anemia, found a decrease in normoblasts in the sternal marrow in all but 3 instances. The marrow findings in the latter cases were observed after improvement in the uremic state. In general, there was an absence of the younger forms of the erythroblastic series and a decrease in the number of erythroid mitoses. In summary, Leitner states that the sternal marrow in nephrogenic anemia shows a hypoplasia and occasionally an aplasia of erythropoiesis. The granulocytes were intact, aside from a slight neutrophillic metamyelocyte and myelocyte shift to the left. The same was true of the megakaryocytic series. In a few cases, eosinophils and plasma cells were seen which might indicate an allergic reaction. With improvement in the kidney lesions and decrease in nitrogen retention, the anemia improved. This, according to Leitner, indicates an aregenerative type of anemia and not an aplastic anemia. In progressive chronic nephritis, the sternal marrow shows progressive aplasia of the erythroblastic picture. The response of the anemia to iron, liver, and arsenic is observed only after improvement of the kidney function. The sternal marrow, therefore, permits the estimation of the tendency towards regeneration or aplasia.

Rohr (1940), Kienle (1942, 1943), Thaddea (1943) and Filo (1937), in their studies of chronic nephritis with anemia, found hypoplasia of the

erythroblastic cells which may be due to a primary toxin or a decrease of the primitive erythroblasts. Thaddea (1943) and Gottsegen (1937) noted that the neutrophilic metamyelocytes and mature granulocytes are always numerous, frequently with a hypersegmentation of the nucleus, whereas the lymphocytes are markedly decreased in the end-stage of uremia. Because of the hypoplastic and aplastic character of the erythroblastic tissue, there is no effect from treatment with iron and liver. Nephrogenic anemia is considered to be a toxic aregenerative anemia in which the influence of the toxic substance is either on formation or maturation of the erythroid tissue in the bone marrow. Vaughan (1936) stated that the pathologic changes of hemopoietic tissues in nephritis are not known in detail. But there is no evidence to suggest any great hyperplasia of erythropoietic tissue. Magner (1938) stated that the anemia occurs regularly in cases of renal insufficiency and nitrogen retention, regardless of the nature of the renal lesions, and that the degree of anemia is usually proportional to the degree of impairment of excretory function of the kidney. This dyshemopoietic type of anemia is due to a deficient production of red blood cells and not to excessive loss of red blood cells by hemorrhage or hemolysis.

Alexeieff (1937) studied renal diseases in patients and experimental uremia in dogs. He concluded that (1) anemia of nephritic patients is a true anemia due to intoxication of the bone marrow by nitrogenous products. The degree of this anemia is found to correspond not to the azotemia of the blood but rather to the duration of the disease. The study of the bone marrow reveals a feeble regeneration of normoblastic type which characterizes an hemopoietic anemia. (2) The leukocytosis which is observed in nephritic patients, just as in patients poisoned by mercury bichloride, is due to a

pronounced regeneration of the myeloid tissue. (3) The number of blood platelets and of megakaryocytes in the bone marrow do not show great modifications. Hemorrhagic symptoms that are observed are not dependent on thrombopenia. (4) The bone marrow cannot be considered as a depot of nonprotein nitrogenous products. (5) Fluctuations in the nonprotein nitrogen content of the blood and bone marrow are roughly parallel.

Wintrobe (1934) drew attention to the similarity of the blood picture in the anemias of nephritis, aplasia of the bone marrow and the anemia which he found in various inflammatory diseases. All were normocytic or microcytic but in none was there a marked hypochromia.

Murphy, Grill and Moxon (1934) stated that in acute nephritis a red cell count below 3.5 millions per cu. mm. implies progressive breakdown of renal function. MacArthur (1942) noted that in chronic hemorrhagic nephritis there is often a severe orthochromic normocytic anemia with a normal or slightly increased number of reticulocytes and mild leukocytosis. The blood was not that of aplastic anemia.

Boyd (1944) stated that the anemia in glomerulonephritis seems to be due to interference with the building up of hemoglobin in the liver, rather than to lack of formation of red cells in the bone marrow. An important factor is diminution or absence of hydrochloric acid in the stomach which interferes with the proper metabolism of ingested food and absorption of iron. Haden (1946) took the viewpoint that anemia of kidney disease is due to a toxic action of retained metabolic products on the marrow. Fowler (1949) shared the opinion of others that the anemia of chronic nephritis is probably due to a toxic depression of the bone marrow as there are but slight evidences of blood degeneration.

Bone marrow studies in chronic nephritis show a tendency for hematopoiesis to be arrested in the erythroblastic stage; hence, the anemia is due to diminished blood production. Castle and Minot (1936), in discussing the anemia of chronic nitrogen retention, concluded that the anemia is due to diminished blood production since there are few signs of regeneration of the red blood cells. They agreed with others that the anemia is due to depressed activity of the hemopoietic tissues. The leukocytes are not always depressed and platelets usually are normal in number. With infection, the leukocytes show a shift towards immaturity of the neutrophils. On the other hand, Schilling (1929) stated that there is no significant alteration in uncomplicated cases of chronic nephritis. Sturgis (1948) accepted the theory that the anemia results from a depressed hemopoietic activity of the red blood cells, forming elements in the bone marrow which in some unknown manner is secondary to severe impairment of renal function. Sturgis did not favor the suggestion of Townsend, Massie and Lyons (1937) that the diminished hydrochloric acid plays any major role in the production of the anemia, although it may contribute to it.

Loge, et al. (1950) concluded that blood loss by hemolysis may be partly responsible for the anemia of chronic renal insufficiency, but the prominent mechanism is an invariable depression of erythropoiesis associated at times with an extracorpuscular hemolytic factor.

Anemia is frequently noticed in uremic states and there appears to be a direct parallel between the severity of anemia and nitrogen retention (Callen, and Limarji, 1950). The anemia observed in nephritis is usually normocytic, normochromic but may at times be microcytic and hypochromic (Callen and Limarji, 1950).

It is not clear how anemia is caused in nephritis. Townsend, Massie and Lyons (1937) revealed that due to the impairment of excretion in chronic nephritis, acidosis resulted. This in turn decreased gastric secretion with resultant hypochlorhydria. In this condition iron is not absorbed and anemia results.

Whipple and Robscheit-Robins (1939) found that in early nephritis hemoglobin production in the dog was approximately 85 percent of normal and in more advanced nephritis 70 percent of normal.

Fouts, Corcoran and Page (1941) remarked that in nephrotoxic nephritis in dogs anemia resulted due to the depression of the activity of bone marrow. This was later corroborated by Loge, Lange and Moore (1950) who found that erythropoiesis was depressed in chronic renal insufficiency.

McManus (1951) contended that microcytic hypochromic anemia in chronic renal condition was a result of the toxic action of accumulated phenols on the bone marrow.

DeWardener (1958) reported that the depression of bone marrow (resulting in anemia) was directly proportional, though not necessarily caused by, the rise in blood urea.

The lack of correlation between symptoms and degree of renal impairment was well demonstrated by the findings of Newburg and Camara (1951) who noticed severe anemia in early nephritis and a low degree of anemia in severe nephritis.

Bonani (1959) reported that in 30 dogs with chronic nephritis there was a marked increase in the hemoglobin content and color index, a slight increase in white blood cells and a decrease in red blood corpuscles.

Respiratory System

Paroxysmal dyspnea (cardiac asthma) may occur as a result of the hypertension present in uremia. Cheyne-Stokes or irregular periodic breathing is common in the terminal stages. These respiratory difficulties have nothing in common with true bronchial asthma. The old terms renal asthma and uremic asthma are misleading and should be dropped, for there is no evidence that uremic intoxication actually causes bronchospasm (Fishberg, 1954).

In far-advanced uremia, especially in chronic renal disease, remarkable pulmonary changes develop (Bass, et al., 1952). They occur in the presence of both left ventricular failure and uremia. Rouhier and Plauchu (1934) pointed out that roentgenologically the pulmonary lesions of advanced uremia generally present themselves as cloudy shadows confined to or most prominent in the inner zones of the lung fields.

Myerson (1927) has observed a peculiar grayish, dough-like coating in the hypopharynx, larynx, bronchi and trachea of eleven patients with uremia.

In patients of any species, a urine-like odor is often present and is diagnostic (Smith and Jones, 1958).

In 16 dogs with uremia caused by nephritis, the most frequent lung changes were pulmonary edema, catarrhal purulent bronchitis and interstitial thickening. In 2 cases fibrin network was observed, and in 2 others pseudo-hyaline membranes had formed in the alveoli (Schiefer, 1960).

As a result of anemia caused by nephritis, a deficiency of hemoglobin per unit volume of blood occurs which in turn give rise to what is known as anemic anoxia (Blood and Henderson, 1963).

The respiratory mechanism is exquisitely sensitive to changes in pH of blood. The slightest reduction in plasma bicarbonate through its decomposition by acid is met by increased pulmonary ventilation in which condition excessive amounts of carbon dioxide are removed from the body by forced breathing. Thus, the acidosis of renal insufficiency results in dyspnea.

Integumentary System

The body coat is rough and dry. The dryness of the skin may be very striking in long-standing chronic interstitial nephritis; it is the cutaneous manifestation of dehydration resulting from compensatory polyurea.

Pruritus may sometimes appear. Scratch marks may result. The pathogenesis of the pruritus is not entirely clear. The pruritus is not due solely to the dryness of the skin, though this may contribute (Fishberg, 1954). It has been suggested that this is due to liberation of ammonia from the action of cutaneous bacterial ureases on the urea of sweat (Sodeman, 1961).

There is an unthrifty and sometimes eczematous appearance to the skin (Canine Medicine, 1962).

Eczematous skin conditions have been observed in the course of various chronic organic diseases. In chronic interstitial nephritis in dogs, squamous, crusted dermatoses may develop bilaterally and symmetrically in the back region. In these cases there is a partial loss of hair; the skin itself is dry, thickened, and forms large folds. Some itchy conditions of the lower parts of the extremities have been associated with mild nephritis (Kral, 1961).

Endocrine System

Primary hyperparathyroidism is more of theoretical than of practical interest to the veterinary pathologist. It may arise as a result of adenomatous or carcinomatous change in the gland, but these neoplastic changes are rare and skeletal complications even more so. Secondary hyperparathyroidism is, however, rather common, especially in dogs, as a result of renal insufficiency; a few such cases are complicated by osteodystrophy of obvious degree, and a larger number have lesser degrees of change in the bones.

The hormone of the parathyroid glands has two main functions; it causes phosphate diuresis and it causes the levels of calcium in the blood to rise. These functions are to be regarded as separate but inseparable; separate because they represent distinct functions at different loci of activity, and inseparable because any dysfunction at one or other locus or any primary alteration in levels of calcium or phosphorus in plasma has secondary effects on the other locus or the other ion.

The parathyroid glands are sensitive to changes in the level of ionized calcium in the serum, and this is probably the basis of their principal homeostatic function. Any change which tends to lower serum calcium causes thereby an increase in activity of the parathyroids in an attempt to restore levels of serum calcium to normal. The calcium-deficient diets which lead to rickets will, if severe enough, cause secondary hyperparathyroidism to complicate the picture. Parathyroid hyperplasia is also a result of excessively high levels of phosphorus in the diet, but whether by causing fecal wastage of calcium or by a tendency to hyperphosphatemia is not clear.

That sustained increments of the level of serum phosphate can cause hyperplasia (and hyperfunction) of the parathyroids is accepted as the principal metabolic defect in this system in renal failure (Brodey, et al., 1961; Dammrich, 1958; Kretzschmar, 1956; Nielsen, et al., 1954; Platt, 1951; Hogg, 1948; Liegeois et al., 1946; Gratzl, 1941). Normally, much phosphate is filtered through the glomeruli and partially reabsorbed from the tubules; in diffuse renal disease with chronic uremia the glomerular filtration of phosphate is reduced and the anion is retained, causing hyperphosphatemia, which in turn causes hypertrophy and hyperfunction of the parathyroids in an attempt to reinitiate phosphate diuresis, and leads to mobilization of skeletal mineral and osteodystrophy. This, no doubt, is an oversimplification of the pathogenetic scheme, but it is not possible to elaborate with much confidence; uremia is attended by a variety of metabolic disturbances and their individual contributions to uremic osteodystrophy cannot yet be assessed. Ultrafiltrates of serum from cases of uremia will not calcify rachitic cartilages in vitro while filtrates of normal serum will, a fact which suggests that in uremia there are "toxic" or metabolic defects in serum in addition to alterations of the ionic product of calcium and phosphate. Variations in the levels of calcium and phosphate in the plasma are not consistent in their direction; phosphate is usually, and perhaps always, increased to or beyond the upper range of normal, and serum calcium levels tend, by antagonism, to be lowered; frequently, however, serum calcium is in the normal range, which is probably attributable to efficient compensation by the parathyroids. The acidosis of uremia may also contribute significantly to the osteodystrophy.

The removal of mineral from bone under the influence of parathormone is performed by the osteoclasts. The rapidity with which these cells differentiate and commence activity is indicated by the increase of numbers and the beginning of resorption within 4 to 6 hours after an experimental injection of parathormone. Also of early onset is a replacement of bone marrow and resorbed bone by young connective tissue in which osteoclasts persist as giant cells for prolonged periods (Jubb and Kennedy, 1963).

Thieme (1955) reported that in 29 dogs with chronic nephritis, the adrenals were rich in lipids and there was generally a picture of adaptation to increased activity. In the pituitary gland eosinophile cells were in the majority, whereas basophile cells were present only occasionally.

Body Fluids

The most important effects of renal insufficiency on the body fluids are (1) generalized edema resulting from water retention, (2) acidosis resulting from failure of the kidneys to rid the body of normal acid products, (3) high potassium concentration resulting from failure of potassium excretion, and (4) high concentrations of the non-protein nitrogens resulting from failure of the body to excrete the metabolic end-products (which is called azotemia).

Water Retention and Edema. When the patient drinks water, in response to his normal desire, the body fluids begin increasing immediately and rapidly. If he takes in no electrolytes at the same time, approximately 5/8 of the water will enter the cells and 3/8 will remain in the extracellular fluids. Thus, a patient with edema in nephritis may have both intracellular and extracellular edema. On the other hand, if the patient

should ingest large amounts of salt along with the water, the edema might be only extracellular because of greatly increased amounts of osmotically active substances in the extracellular compartments.

Acidosis. Most uremic patients with renal insufficiency have acidosis. The occurrence of acid intoxication in renal insufficiency was first indicated by the finding of von Jaksch (1888) that the titrable alkalinity of the blood is diminished in uremic patients. Long after, this observation was supplemented by the demonstrations of Straub and Schlayer (1912), Peabody (1915) and others that the carbon dioxide content of the alveolar air is often abnormally low in uremia. That the actual hydrogen ion concentration of the blood may be increased in uremia was indicated by the studies of Poulton and Ryffel (1913) on the oxygen-combining curve of the blood, which showed that the blood of some uremic dogs takes up oxygen with abnormal difficulty.

Uremic acidosis results partly, but not entirely, from the inability of the kidney to excrete adequately the end-products of metabolism, which are usually predominantly acid. Straub (1921) pointed out that when renal insufficiency is present the reaction of the organism is dependent on the ingested food, for if the patient with insufficient kidneys eats food with acid end-products he becomes acidotic, while if the catabolic products are alkaline, alkalosis results.

In recent years, there has been extensive study of the distrubances in acid-base equilibrium resulting from renal insufficiency, which has revealed that uremic acidosis is of complicated pathogenesis, as yet by no means completely elucidated. It has become clear that both decreased glomerular filtration and impaired tubular function are concerned in the

production of uremic acidosis. The inadequate glomerular filtration results in the retention of the predominantly acid intermediary and end-products of protein catabolism, including both inorganic anions and organic acids. On the other hand, the impairment of tubular function causes loss of fixed base because of inability to excrete a urine of acidity as high as normal and deficient ammonia formation.

Marriott and Howland (1916) believed that phosphate retention is a very important factor in the production of uremic acidosis, for about ninety percent of the phosphate in an average urine is acid phosphate. Schmitz, Rohdenburgh and Meyers (1926), as well as Fetters (1923), observed that in all instances of renal insufficiency in which the inorganic phosphate of the blood is increased the carbon dioxide combining power of the blood is lowered, that is to say, there is acidosis. But in other cases they noted acidosis in the absence of phosphate retention, showing that the latter is not the only cause of the acidosis of renal insufficiency. In fact, the investigations of Peters and his co-workers show that phosphate retention is quantitatively a minor factor in the production of uremic acidosis. Marrack (1923) also found that retention of other anions play a larger part in causing the acidosis than does phosphate. One of these has been shown by Loeb and Benedict (1927) to be sulphate. In some instances there is also increase in the concentration of chloride ions, but much more often, particularly when there is vomiting, chloride is decreased in the blood and therefore militates against acidosis.

The significance of retention of organic acids in the blood has been extremely investigated and debated. Straub (1924) calculated that the quantity of known acids retained does not suffice to account for the acidosis

and advanced the opinion that considerable amounts of unknown acids must be held back, which he surmised to be products of intermediary protein metabolism. However, Hartmann and Darrow (1928) believed that they are able to account for practically all the anions present as known substances. The careful studies of Briggs (1932) are in accord with this view. Other investigations, on the contrary, indicate strongly that retention of organic acids is sometimes actually of importance in the genesis of uremic acidosis. Thus, Peters and his co-workers bring evidence that in the terminal stages of uremia ketonic acids may accumulate in the blood. Becher, Enger and Herrmann (1932) found that in renal insufficiency there is accumulation of ether-soluble organic acids in the blood.

It seems plausible that the nature of the retained substances participating in the genesis of renal acidosis varies in the different stages of renal insufficiency. According to this conception, the role of the organic acids would become significant only in the terminal stages when there is "toxic" acceleration in the breakdown of body protein with the result that high concentrations of intermediary products of protein catabolism are liberated and retained because of the renal failure.

In renal insufficiency the kidney is unable to form a urine of hydrogen ion concentration as high as in health. The beautiful experiments of Pitts, et al., (1948, 1950, 1945) have shown that a large part of the acidity of the urine is due to formation by tubular cells of hydrogen ions (perhaps through hydration of carbon dioxide to carbonic acid by carbonic anhydrase), which are then exchanged for ions of sodium and other fixed base in the tubular fluid. When tubular function is impaired, the liberation of hydrogen ions is decreased with resultant diminution in the acidity of the urine and

loss of the ions of fixed base which would otherwise have been exchanged for the hydrogen ions. The consequence is depletion of the fixed base of the blood.

With impairment of tubular function, ammonium ions can not be produced in as great amount as in health. Gamble and his associates showed that while a healthy subject increases his urinary ammonia output in response to administration of an acid-producing salt, an experimental dog with renal insufficiency does not do so. The result is sacrifice of an equivalent amount of fixed base, which tends to deplete the blood alkali and favors acidosis.

The relative importance of decreased glomerular filtration with its entailed retention of anions and tubular insufficiency with consequent cation waste doubtless varies in different forms and stages of renal disease.

In some cases the acidosis thus produced is compensated by hyperventilation and other mechanisms, so that the hydrogen ion concentration of the blood remains normal despite the hypocapnia. But in other instances compensation is incomplete and the hydrogen ion concentration of the blood rises; in such cases the pH of the blood has been observed to be as low as 7.04 (Peabody, 1915; Schmitz, Rohdenburgh and Myers, 1926).

Vomiting with resultant loss of hydrochloric acid often combats uremic acidosis to a greater or less extent. In fact, on some occasions enough acid may thus be lost to produce an actual alkalosis. Harrison and Perlzweig (1925) published a paper on investigation, seemingly of this variety, in which the pH of the blood rose to 7.6. That this does not occur more frequently is apparently due to the fact, observed by Peters and his collaborators, that the vomitus in uremia often contains little free hydrochloric acid.

Uremic acidosis may be of the utmost severity when the carbon dioxide combining power of the blood is sinking as low as ten volume percent. Chace and Myers (1920) considered that the acidosis may be severe enough to be the immediate cause of death.

Elevated Potassium Concentration. The degree to which the potassium concentration increases depends principally on the rate of protein metabolism after nephritis has occurred, The breakdown of the cellular proteins releases potassium from combination with the proteins, and the extra potassium then passes into the extracellular fluid. Obviously, failure of the kidney to excrete the potassium as it is released will cause an elevated potassium concentration in the extracellular fluid when the potassium concentration rises to 10 m. eq./l. it is likely to stop the heart in diastole.

Increase in Non-protein Nitrogens (azotemia) Following Nephritis. The non-protein nitrogens include urea, uric acid, creatinine, and a few less important compounds. These, in general, are the end-products of protein metabolism and must be removed from the body continually to insure continued protein metabolism in the cell but in nephritis they are retained in the body fluids.

Special Senses

The eyes have an anxious appearance and their conjunctiva are congested due to severe venous congestion with high venous pressure (Canine Medicine, 1962). Retinitis may be present which is correlated with hypertension and not due to renal insufficiency (Fishberg, 1954).

SUMMARY

In general, diseases of the kidney can be classified into three distinct categories, namely, degenerative (nephrosis), inflammatory (nephritis) and vascular (arteriosclerotic). The most common renal inflammatory disease in man is glomerulonephritis, while interstitial nephritis is of minor significance. In the dog, interstitial nephritis is of paramount importance, while glomerulonephritis is of little account. A perusal of the literature, both medical and veterinary, indicates that Bright's disease has been well studied, while interstitial nephritis, with few exceptions, has been only superficially examined. Nephritis is the most important and frequent among the affections observed in the urinary tract of the canine species. The importance of this condition lies in its frequent occurrence and its deleterious consequences on the other body systems of the dog.

The principal renal inflammatory disease of the dog is interstitial nephritis which may be acute, subacute or chronic. Interstitial nephritis was first described by Davis. Most old dogs show some kidney damage in the normal course of living. The following organisms have been found associated with nephritis: E. coli, Proteus vulgaris, streptococci, pseudomonas, Aerobacter aerogenes.

The most common type of renal failure and uremia results from chronic renal disease. It causes depletion of plasma potassium with resultant weakness and paresis of skeletal muscles. Muscular twitching and far less usually, convulsions are thought to be caused by a decrease in the ionized calcium of blood due to renal retention of phosphate. The tendency towards depression of ionized calcium acts as a stimulus for parathyroid hyperplasia,

which is manifested functionally and structurally. Functionally it results in decalcification which leads to the disease entity known as renal osteodystrophy (rubber jaw), which is primarily a nephritic condition with bone lesions, particularly of the skull, appearing later. If this condition occurs in young individuals before full growth is reached, it is called renal rickets, or renal dwarfism. The parathyroid hyperplasia, together with the acidosis, which often is associated with the kidney dysfunction, will cause osteomalacia by mobilization of calcium and phosphorus from the skeleton in an effort to maintain a normal serum calcium, with formation of soft, rubbery bone.

In the dog, the clinical signs of bone resorption are confined to the jaws and the head, and thus the term "rubber jaw" is often ascribed to this disease by clinicians. Actually, there is generalized osteoporosis of all the long bones on histopathological examination.

Primary hyperparathyroidism is more of theoretical than of practical interest to the veterinary pathologist. It may arise as a result of adenomatous or carcinomatous change in the gland. Secondary hyperparathyroidism is, however, rather common, especially in dogs, as a result of renal insufficiency; a few such cases are complicated by osteodystrophy of obvious degree, and a larger number have lesser degrees of change in the bones. That sustained increments of the level of serum phosphate can cause hyperplasia (and hyperfunction) of the parathyroids is accepted as the principal metabolic defect in this system in renal failure.

When the accomplishment of the kidneys falls behind the needs of the organism, potential urinary constituents accumulate in the blood. Among the potential urinary constituents are nitrogenous end-products of protein

catabolism which have no significant extrarenal avenue of elimination. The result is rise in the non-protein nitrogen of the blood. The retained urinary constituents may cause secondary changes in the chemical composition of the blood. Thus phosphate retention tends to lower the calcium content of the blood. The retention of fixed acid depresses the blood bicarbonate. This uremic acidosis results partly, but not entirely, from the inability of the kidney to excrete adequately the end-products of metabolism, which are usually predominantly acid.

The association of anemia with renal diseases has long been recognized and various causes for the anemia have been suggested. Among them defective blood formation has been considered to be an important factor in the production of anemia. There is a direct parallel between the severity of anemia and nitrogen retention. The anemia observed in nephritis is usually normocytic, normochromic, but may at times be microcytic and hypochromic.

Generally, in uremia caused by nephritis, the heart is subjected to various adverse influences. When uremia supervenes in chronic renal disease, hypertension and left ventricular hypertrophy usually are already present and show the strain to which the left ventricle is subjected, In acute renal disease, hypertension and uremia may evolve concomitantly, or either may precede the other. Effects of acute and chronic nephritis upon the structure of the cardiovascular system are of two main types: (1) those due to hypertension, seen only in dogs with chronic nephritis; (2) necrotizing lesions in the heart and great vessel, mainly in dogs with acute nephritis and scars at these same sites in dogs with chronic nephritis. Blood pressure is also raised in chronic nephritis in dogs.

Paroxysmal dyspnea (cardiac-asthma) may occur as a result of hypertension present in uremia. Nephritis may also result in pulmonary edema, catarrhal purulent bronchitis and interstitial thickening.

In chronic interstitial nephritis in dogs, squamous, crusted dermatoses may develop bilaterally and symmetrically in the back region. In these cases there is a partial loss of hair; the skin itself is dry, thickened, and forms large folds.

Anorexia, nausea and vomiting are common in uremia and occasionally constitute the first symptoms of renal disease. Although constipation is more common, diarrhea often bloody, tends to appear in the later stages of renal failure. The cause of the gastrointestinal disorders is not clear.

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THE EFFECT OF NEPHRITIS ON OTHER BODY SYSTEMS OF THE CANINE

by

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AN ABSTRACT OF A MASTER'S REPORT

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MASTER OF SCIENCE

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Nephritis is the most important and frequent among the affections observed in the urinary tract of the canine species. The importance of this condition lies in its frequent occurrence and its deleterious consequences on other body systems of the dog.

Interstitial nephritis is most common in the canine species. In acute interstitial nephritis anorexia, polydipsia and vomiting are frequently observed. Temperature elevation is moderate to brief.

In chronic interstitial nephritis the coat is rough and the animal is dehydrated. The patient voids large amounts of pale, watery urine (polyuria).

Significant degrees of chronic interstitial nephritis results in uremia which in turn exerts its deleterious effects on various other body systems of the dog.

Anorexia, nausea and vomiting are common in uremia, and occasionally constitutes the first symptoms of renal disease. The cause of gastrointestinal disorders is not clear.

Effects of acute and chronic nephritis upon the structure of the cardiovascular system is of two main types: (1) those due to hypertension, (2) necrotising lesions in the heart and great vessels, mainly in dogs with acute nephritis, and scars at these same sites in dogs with chronic nephritis. Pericarditis occurs in the terminal stages, indicating almost invariably that the end is near.

The neurological symptoms usually range from depression, weakness, and drowsiness to a comatose state, although muscular twitchings of a fibrillary type sometimes occur.

The parathyroid hyperplasia caused by chronic nephritis, together with the acidosis, which often is associated with the kidney dysfunction, will cause osteomalacia by mobilization of calcium and phosphorus from the skeleton in an effort to maintain a normal serum calcium, with formation of soft, rubbery bone. In the dog, the clinical signs of bone resorption are confined to the jaws and head, and thus the term "rubber jaw" is often ascribed to this disease by clinicians.

Nephritis results in anemia due to intoxication of the bone marrow by the retained nitrogenous products.

Anemia caused by nephritis results in anemic anoxia. The acidosis of renal insufficiency is met by increased pulmonary ventilation in which condition excessive amounts of carbon dioxide are removed from the body by forced breathing.

The body coat is rough and dry. The dryness of the skin may be very striking in long-standing chronic interstitial nephritis; it is the cutaneous manifestation of dehydration resulting from compensatory polyuria.

That the sustained increments of the level of serum phosphate can cause hyperplasia and hyperfunction of the parathyroids is accepted as the principle metabolic defect in this system in renal failure.

The most important effects of renal insufficiency on the body fluids are (1) generalized edema resulting from water retention, (2) acidosis resulting from failure of the kidneys to rid the body of normal acid products, (3) high potassium concentration resulting from failure of potassium excretion, and (4) high concentrations of the non-protein nitrogens resulting from failure of the body to excrete the metabolic end-products.

The conjunctiva of eyes are congested due to severe venous congestion.