AN EXPERIMENTAL AND CRITICAL STUDY OF THE ETIOLOGY OF CHRONIC NEPHRITIS.*

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"It is only when the full etiology of disease is known that the medicine of our day can become the medicine of the future—that is to say, hygiene in its widest sense."—PAWLOW.

CONTENTS.

Introduction—Methods—Selection of material—The effect of alcohol, ether, chloroform and amyl nitrite inhalations—The effect of injury of the kidney by the hypodermic needle, and of normal saline solution, adrenalin and alcohol solutions injected directly into the renal parenchyma—The effect of adrenalin and gelatin solutions injected directly into the veins—Summary of experimental results—Discussion on the etiology of chronic nephritis—Conclusions—Bibliography.

INTRODUCTION.

With the knowledge that the combined death rates from heart and kidney diseases have almost doubled within the past twenty-five years in the cities of Boston, New York and Chicago,¹ there has been offered no sufficient explanation for the cause of this increase, or of the widespread occurrence of nephritis, and no means of prevention are proposed offering any hope that the increase will be checked in the future. Without knowledge of the cause of disease, little of permanent value has ever been done toward its prevention, if one might except the discovery of vaccination for the prevention of smallpox.

While a variety of substances have been used successfully to cause diseased conditions in the kidneys of animals, such as mineral or vegetable poisons or irritants, the toxins of pathogenic bacteria, and nephrotoxins, at present the lesions reported and the conditions created can not be claimed to resemble essentially the lesions of chronic productive nephritis in man, which are found so frequently at autopsy that a normal kidney is a rare exception in an adult.

Recognizing that the accepted etiologic factors mentioned and copied from author to author, from the time of Richard Bright, account for many of the frankly-marked cases which can be followed in an almost unbroken chain of clinical and pathologic evidence from the inception

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1. Darlington: New York Med. Jour., 1907, lxxxv, 1158.

of the disease until death, there remain unexplained the causes of cases of so-called initial nephritis. Chronic inflammatory processes in the kidney are so commonly found at autopsy when there has been no reason to suspect nephritis before death,² that we must add many cases of unrecognized nephritis to those which are recognized but which lack sufficient etiologic explanation.

While a variety of causes are known to be responsible for, or to contribute to, the occurrence of chronic interstitial or productive inflammation in various tissues, circulatory disturbance resulting in a stagnation of venous blood or a diminution in the supply of arterial blood, or both, is an almost constant accompaniment, and may in some instances be shown to be the sole cause of the accumulation of connective tissue to the permanent and increasing detriment of the functional activity of the tissue or the organ involved.

The means at our disposal to effect changes in the blood supply of the kidney are few and offer many obstacles in the way of drawing accurate conclusions. The facts given here are based on experimental conditions produced in fourteen dogs over a period of twenty-six months, the plan of tests and observations being outlined in the preceding summary.

METHODS.

Small and medium-sized dogs were used for the experiments. It was found necessary to test the urine of dogs selected, over a period of three months, to eliminate those in which occasional or persistent albuminuria indicated a probable spontaneous or rather existing nephritis of unknown origin.³ During this period of probation the dogs were kept in large cages, where they had full freedom of movement, and from which they were released at least every second day to run about for a short time, either in the building or in the yard outside. Their diet during this period was water and Spratt's dog biscuit. In selecting the fourteen dogs that were finally used, eleven were rejected because of albuminuria. The prevalence of albuminuria in dogs used for experimental purposes and the need of care in selecting material has been noted by Pearce³ but so far as I can find there is no mention of such precautions being taken by any other experimenters with dogs or other animals. Inasmuch as removal of a piece of the kidney for diagnostic purposes, before the tests are begun, does not give reliable information as to an existing nephritis, and, moreover, as such a procedure, as will be shown later, tends to the production of such lesions as are being sought for by other

2. Emerson, C. P.: Jour. Am. Med. Assn., 1906, xlii, 5, 89.

3. Pearce: Univ. Penn. Med. Bull., 1903-4, xvi, 217.

means, we must rely on the urinary examinations as the best, though certainly not a perfect, test for the presence of a nephritis. As Pearce³ has shown, and as will be shown in the following tests, nephritis may exist in dogs without albumin or casts being constantly or at any time present in the urine.

The dogs that were finally selected were kept continuously on the diet described above, with occasional changes to meat diet, for periods of a week or two every six months. All but three of the dogs suffered from mange at one time or another while they were under observation, and most of them recovered completely from it by the application of 10 per cent. sulphur ointment to the skin. Several of the dogs had attacks of diarrhea, which were checked by a dose of castor oil and a diet of milk.

Three classes of test procedures were used: (A) inhalations, (B) hypodermic injections into the kidney substance, and (C) hypodermic injections into the veins or the muscles of the legs.

(A) INHALATION METHOD.

Alcohol, ether, chloroform and amyl nitrite were used to see if the repeated use of general vasodilators would produce any appreciable changes in the functions or structure of the kidney. The dog was placed in an air-tight wooden box, provided with two glass windows in the top, and an entrance tube for air at one end connecting directly with the supply flask, and an exit tube for air at the other end, provided with a mica valve so adjusted as to prevent the entrance of air, but allowing air to pass out when the pressure in the box was only slightly over atmospheric pressure.

The supply flask was connected by a one-half inch rubber tube with the entrance tube of the box by one opening, and to the tube of an artificial respiration apparatus by the other opening. A third and very small tube, with a stop-cock, in the cork of the supply flask allowed of the administration of the desired amount of the drug to be used. The flask was immersed in a pail of water, which was kept at a temperature of from 30° to 35° C. during alcohol administration, and at from 17° to 20° C. when ether, chloroform and amyl nitrite were being given.

Air was supplied by an artificial respiration apparatus at the rate of 35.5 respirations a minute, and each inspiratory blast had a volume of 400 c.c. Thus the dogs were supplied with 14,200 c.c. of air a minute. As the air passed into the supply flask and out of it into the box it carried with it some of the vapor of the drug to be administered. Knowing the time taken in evaporating the volume of the drug put into the supply bottle, and the amount of the drug and of the air supply being known.

it was found that the percentage of the drug present in the air which the dog breathed was as follows:

For alcohol during 30 minutes	.01765	per cent.
For ether during 30 minutes	.03521	per cent.
For chloroform during 30 minutes	.007	per cent.
For amyl nitrite during 15 minutes.....	.0018	per cent.

There was little or no struggling of the animals in the box, as the administration of the drugs was gradual, and after a few treatments the dogs usually kept perfectly quiet and relaxed on the floor of the box.

The respirations and the color of the nose and lips could be watched through the windows in the box, and indications of failing circulation were met by opening the box or by connecting the air supply tube directly with the entrance tube of the box, cutting out the supply flask from the circuit. Squibb's ether, and chloroform, and amyl nitrite were used, and absolute alcohol was used. After the treatment was finished the dog was allowed to recover gradually from the effect of the drug, and when muscular co-ordination was restored he was taken to the cage again.

(B) HYPODERMIC INJECTIONS INTO THE KIDNEY SUBSTANCE.

The skin was shaved over the lumbar region on the left side and then washed over with 95 per cent. alcohol. The kidney was then fixed as well as possible with one hand, and a long hypodermic needle was passed through the skin and lumbar muscle until the kidney was felt. The needle point was then passed through the capsule and the dose of the drug injected. This procedure was not always successful, but tests on the cadaver, and on many dogs which were used for other purposes, and observed with the kidney and needle *in situ*, make me feel confident that the majority of attempts were successful.

To control these tests two dogs were used in which no drug was given. In one the needle was simply inserted into the renal parenchyma and withdrawn, and in the other 6 c.c. of normal saline solution were injected into the kidney substance. The alcohol and adrenalin chlorid solutions were used to test the possibility of affecting the blood supply of the kidney locally without injuring the parenchyma primarily. The alcohol was used in 25 per cent. strength in normal salt solution, and the adrenalin chlorid was used in 1 to 1,000 solution.

(C) INTRAVENOUS INJECTIONS.

The veins of the leg were used and aseptic precautions were observed. A 10 per cent. aqueous solution of acetate of lead was used to obtain a standard type of chronic toxic nephritis. A 1 to 1,000 solution of

adrenalin chlorid was used to see if general vasoconstriction would produce any secondary results in the kidney. A 5 per cent. solution of gelatin in water, which was fluid at body temperature, was used to test the effect of persistently increased viscosity of the blood upon renal function and structure, the gelatin being injected through a warmed syringe with a small aspirating needle.

URINARY TESTS.

The urine was collected at intervals during the course of treatment, the dog being kept in a metabolism cage for a day or two for the sake of obtaining a clean sample of urine. The urine was tested as to its specific gravity, for albumin by the use of heat and nitric acid, and microscopically for casts. It may be properly noted here that casts were not found in any case.

HISTOLOGIC MATERIAL.

At the autopsy specimens of the various organs were hardened in equal parts of Mueller's solution and 5 per cent. formalin and were later washed, imbedded in celloidin, sectioned, stained in hematoxylin and eosin, and mounted in balsam.

A. EFFECTS ON THE KIDNEY OF REPEATED GENERAL VASOMOTOR DILATATION.

ALCOHOL.

In spite of the disagreement among physiologists and among clinicians as to the position alcohol holds in nutrition, there is substantial agreement as to its effect on the circulation. The best summary of results is found in the recent observations of W. E. Dixon,⁴ who reaches the following conclusions.

"Alcohol does not affect all the vessels in the intact animal in the same way.

"Alcohol dilates the vessels of the skin rapidly, and tends to constrict the vessels in muscle tissue, and to a less marked degree in the splanchnic area, large doses causing immediate splanchnic constriction.

"The usual effect in man is a central one, causing superficial dilatation and internal constriction. This is the reaction of the organism against the rise of temperature which the increased metabolism would otherwise result in. Central stimulation (or stimulation of the corpus striatum) causes increased metabolism.

"The sum total of general pressure changes due to alcohol is usually a vasodilatation."

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4. Dixon: *Jour. Physiol.*, 1907, xxxv, 346.

We may suppose, therefore, that the frequent administration of alcohol to an animal would subject the kidney to fluctuations in its vascular supply. Periods when there was a decided decrease in the blood bulk passing through the kidney, owing to a lowered general pressure and constriction of the splanchnic vessels, would result.

PROTOCOL 1.

Dog.—White male fox terrier; weight, 8290 G. Urine, free from albumin and casts; specific gravity, 1013. Diet, dog biscuit and water. Probation period, July 1 to Sept. 15, 1905. Normal respiration and pulse at rest, 20 and 100.

Alcohol was administered by the inhalation method at intervals of a few days from Sept. 5, 1905, to March 17, 1906, the doses varying from 25 c.c. to 60 c.c., and the total amount of absolute alcohol used being 700 c.c. The duration of muscular incoordination averaged two hours at each administration. A marked and unexpected result of this method of administering alcohol was the extreme rapidity of respiration and the change in the pulse-respiration ratio. At the height of the effect, usually at the end of fifteen minutes, the respirations increased to from 220 to 260 a minute, and when on several occasions the dog was removed from the box for better observation of this phenomenon, the pulse was found to be from 120 to 130 a minute, the respirations remaining at 220 or more. This was in no way to be mistaken for dyspnea, as the tongue and nose were pink and the rapid respirations persisted for some minutes after the dog was removed from the inhalation box. Furthermore, neither this dog, nor the others tested in the box, showed any evidence of dyspnea when supplied with air alone, and in all probability this was a manifestation of excessive central irritation.

March 17, 1906: Weight, 9,300 G.; appears in good condition, has had no mange; urine contains marked traces of albumin, specific gravity 1020. April 28, 1906, the dog died, having had general muscular spasms several times a day for the past week; death in tonic convulsion; weight, 7940 G.

Autopsy.—No edema of the body, but dilatation of superficial capillaries; no fluid accumulations in the pleura, pericardium or peritoneum. Heart distended and enlarged. Lungs deeply congested. Kidneys soft, swollen and congested.

Histologic Examination.—The heart muscles and aorta show no changes from normal structure. The lungs show intense engorgement with a few areas of pneumonic consolidation in what would correspond to the stage of red hepatization. There is no connective tissue increase in the lungs. The liver cells are poorly defined, take the stain poorly, and there are a few small areas of necrosis in the parenchyma. There is no increase in the connective tissue. The kidneys present the picture of severe chronic degeneration. The capsule is much thickened and there is an extension of the recently forming new connective tissue from the inner layers of the capsule into the cortex of the kidney. Here we find compression of the superficial tubes. The glomerular tufts are, for the most part, distended and the tuft cells increased in number. Elsewhere the glomeruli share in the general parenchymatous degeneration. It is difficult to find any normal tubules, straight or convoluted. The degeneration has not been of sufficient duration to allow of replacement fibrous formation, although small areas of round-celled connective tissue are found in the cortical layer.

ETHER.

The vasodilatation caused by ether is one of its marked effects on the vascular system, and its repeated use might be expected to cause some injury to the function of various tissues, as the result of the general low-

ering of blood pressure, apart from the accepted irritant effect it has upon the kidneys and lungs during and immediately after its administration.

PROTOCOL 2.

Dog.—Black and white male fox terrier; weight, 6100 G. Probation period from April 28, 1905, to Sept. 9, 1905. No albumin or casts in the urine; specific gravity ranged from 1028 to 1038. Respirations from 20 to 24, pulse from 90 to 100. Ether was administered by inhalation method at frequent intervals from Sept. 9, 1905, to March 24, 1906, the doses varying from 90 to 200 c.c., and the total amount used being 5590 c.c. The duration of the effect of the drug in each instance was from 20 to 60 minutes. The pulse was increased from 180 to 200, and the respiration to from 36 to 44 in the minute. Cyanosis did not occur, and the skin, though warm and pink, did not show any marked vasodilatation during treatment.

March 24, 1906: Weight, 7340 G.; in perfect condition; no albumin or casts in the urine.

Feb. 22, 1907: During the past year the dog has been in uniformly good condition, on the diet as described; no albumin or casts have been found in the urine; weight 7210 G.

July 19, 1907: Still in the best of condition; weight 7210 G.; no albumin or casts; killed by destroying medulla with a knife, i. e., by "pithing."

Autopsy.—No abnormal appearances in any organs.

Histological Examinations.—Heart, liver and aorta present no abnormal microscopic appearances. The kidneys show a marked chronic inflammation, characterized by moderate thickening of the capsule in a few places, with a slight increase of connective tissue cells from the surface of the capsule into the cortex of the kidney, and a free subcapsular vascular network. The cells of the glomerular tufts are increased in size and number, and the capsular cells are in some instances increased. There are numerous small areas of connective tissue of comparatively recent formation, and in no instance have they resulted in contraction of the tufts after a resulting atrophy. The tubular epithelium is swollen, but not degenerated. The appearance would suggest a chronic productive nephritis, resulting from chronic congestion.

CHLOROFORM.

Chloroform inhalation causes a fall in general blood pressure and, according to Thompson,⁵ an increase of blood flow through the glomeruli of the kidney, a prolonged administration resulting in a vascular stasis in the glomerular vessels. In other words, aside from its effects as a protoplasmic poison, which chloroform has on all tissues, it causes a general low blood pressure throughout the body, and a greater or less congestion of the kidney according to the depth of the narcosis. Embley and Martin⁶ explain the effect of chloroform inhalation from 1 to 3 per cent. vapor as due to a paralysis of the neuromuscular mechanism of the renal vessels, which they say accounts for most of the fall in general blood pressure always noted in chloroform narcosis.

5. Thompson: Brit. Med. Jour., 1906, i, 608.

6. Embley and Martin: Jour. Physiol., 1905, xxxii, 147.

PROTOCOL 3.

Dog.—Brown and white male fox terrier; weight, 6400 G. Urine, specific gravity, 1024; no albumin or casts. Normal respiration, 22; pulse, 90. Probation period from April 28, 1905, to Sept. 16, 1905; mange during the summer, cured by September 16. Chloroform was administered by inhalation from Sept. 28, 1905, to March 24, 1906, at frequent intervals. The dose varied from 30 to 40 c.c. at each treatment, the total amount used being 1280 c.c. The duration of the effect of the drug varied from 45 to 75 minutes at each treatment; the pulse was increased to 96 or 100; respiration decreased to 12 or 14 in a minute. Occasionally it was necessary to use artificial respiratory movements, with the dog removed from the box, to accomplish resuscitation from the occasional collapses, which the free use of chloroform sometimes brought on.

Feb. 1, 1906: Weight, 6770 G. Appears to suffer from some urinary irritation. Urine, specific gravity, 1044; heavy traces of albumin.

March 24, 1906: Weight, 8050 G. In fine condition; urine free from albumin and casts; specific gravity, 1055.

Nov. 22, 1906: Died; weight, 6040 G.; had been failing in strength for some time past; no mange. Except for an apparently enlarged heart there is nothing noticeable at autopsy except marked emaciation.

Histologic Examination.—Heart muscle, aorta and liver normal. Lungs show considerable collections of black granules surrounded by connective tissue. Many of the alveolar cells include foreign particles. The kidneys show swelling and hypertrophy of the tuft cells and some proliferation of the capsular cells about the glomeruli. The kidney capsule shows no changes. The tubules show a moderate cloudy swelling, and the lumen in some instances is filled with granular detritus. There is no new connective tissue formation.

AMYL NITRITE INHALATION.

Amyl nitrite acts directly on the muscular coat of the blood vessels and causes a wide dilatation. The formation of methemoglobin, which occurs rapidly, prevents the use of amyl nitrite over long periods and was the cause of death in one of the tests to be described. It was thought probable that repeated alterations in the general blood distribution of the body, caused by amyl nitrite, might affect the kidneys.

PROTOCOL 4.

Dog.—Brown and white male fox terrier; weight 7050 G. Urine, specific gravity, 1030; no albumin or casts. Normal respiration, 16; pulse, 96. Probation period from May 24, 1905, to Sept. 11, 1905. Amyl nitrite was administered at intervals from Sept. 11, 1905, to Feb. 6, 1906, in doses of from 2 to 7 c.c. each, the total amount used being 170 c.c., the effect lasting from 20 to 40 minutes. Vomiting, dizziness and apparently delirium occasionally accompanied recovery from the use of the drug.

Feb. 4, 1906: Urine free from albumin and casts; specific gravity 1050; weight, 6730 G.

Feb. 6, 1906: After being in the box ten minutes with a dose of 4.5 c.c. the dog collapsed and could not be resuscitated from the extreme cyanosis and urgent dyspnea which shortly terminated in death.

Autopsy.—This revealed a blanched surface, deep (methemoglobin) cyanosis of mucous membranes, muscles pale and purplish red, heart intensely engorged, lungs collapsed and pale, liver deeply congested, kidneys tense and deeply congested, stomach and bowels empty.

Histologic Examination.—The heart and lung specimens were spoiled in the hardening fluid and could not be cut. The liver shows general capillary distention and engorgement. The two kidneys appear intensely congested. The glomerular tufts are distended with blood. The tubules almost uniformly are separated from one another by capillary vessels full of red blood cells instead of appearing to be in direct contact which is usually the case, i. e., the entire capillary network of the kidney appears engorged without any change in the parenchyma or capsule. There is no new connective tissue formation. This picture of acute congestion would certainly be expected from the cause and manner of death.

PROTOCOL 5.

Dog.—White and brown mongrel male, 8350 G.; no albumin or casts in urine; specific gravity 1014. Probation period from June, 1905, to Nov. 4, 1905. Amyl-nitrite was administered from Feb. 8, 1906, to March 24, 1906, in doses of 3 c.c. each to a total of 50 c.c. The effects were similar to those observed in the dog of Protocol 4.

Feb. 26, 1907: Weight 8940 G.; trace of albumin, general condition good.

July 1, 1907: Weight 7500 G.; dog died after a period of gradual failure of appetite and nutrition without convulsions or other appearances of disease.

Autopsy showed no gross evidences of disease except an unusually flabby heart muscle and congested lungs.

Histologic Examination.—The heart, liver and lungs are normal. The kidneys show moderate thickening of the capsule, but no tendency to connective increase or the formation of wedges in the kidney parenchyma. There is distinct, though not extensive increase in the glomerular tuft cells, and in a few instances a flattening or atrophy of the capsular cells. The tubules are in some places markedly degenerated as shown by the granular and non-nucleated condition of the cells, the abundant granular detritus in the lumen, and the absence of clearly defined cell outlines. A few areas in the outer layer of the cortex show young round celled connective tissue formation.

SUMMARY A.

1. The inhalation of alcohol has caused chronic degeneration of the kidneys with a beginning connective tissue replacement.
2. The inhalation of ether has caused a chronic productive nephritis, in which we find a swelling of the tubular epithelium, increase in the size and number of the glomerular tuft cells and areas of connective tissue formation.
3. The inhalation of chloroform has caused some interference with the nutrition of the glomerular and tubular cells, resulting in a moderate swelling and degeneration.
4. The inhalation of amyl nitrite has caused in one instance death with marked visceral engorgement and intense renal congestment, and in another instance we observe a moderate degeneration of the tubular epithelium and a connective tissue formation.
5. The three dogs which had been subjected to alcohol, chloroform, and amyl nitrite inhalation a considerable time before their death, died under such conditions as to make one suspect an error in nutrition and elimination, and the pathologic findings, although not conclusive, sug-

gest that the condition of the kidneys was probably responsible for their deaths.

6. The facts that the four dogs, which survived the prolonged treatment by inhalation of the various drugs, gained in weight and maintained apparently excellent health up to the time the treatment was discontinued, and that the symptoms of failure in nutrition occurred some months later, argue for the probability that none of the drugs caused acute degenerative changes at the time of their administration, as they are known to do when given in large doses, but that the repeated disturbances of circulation which all these drugs effect resulted finally in the various grades of chronic degeneration, followed or not by chronic productive nephritis, which were found at autopsy.

B. EFFECT ON THE KIDNEY OF MECHANICAL INJURY OF ITS SUBSTANCE AND OF VARIOUS DRUGS INJECTED DIRECTLY INTO ITS SUBSTANCE.

ALCOHOL.

Alcohol was used in two dogs, in one in 50 per cent. strength and in the other in 25 per cent. strength, with the expectation that a coagulation of the kidney substance might occur at the site of the injection, which would so interfere with the nutrition of the kidney that a general nephritis would result.

PROTOCOL 6.

Dog.—White and black male fox terrier, weight 9110 G. Urine free from albumin and casts throughout a four-month probation period as described above. Between January 11 and 31, 1906, ten injections of 50 per cent. alcohol of 4 c.c. each were made into the left kidney. No albumin was found in the urine of this dog at any time.

Feb. 8, 1907: The dog died, weight 5880 G.; it had been failing in strength for some time past although taking large amounts of biscuits and water and not suffering from diarrhea or vomiting. No convulsions.

Autopsy.—Emaciation severe; right kidney pale, smooth, normal; left kidney deep purple, scarred and intimately adherent to the lumbar muscles. The heart, aorta, liver and lungs appear normal.

Histologic Examination.—The heart, aorta and liver appear normal. The lungs show slight capillary congestion. The right kidney has a normal capsule and parenchyma. The left kidney shows advanced and extensive, chronic inflammation, most severe at the point of dense renomuscular adhesions and extending in a wide area of obliterating connective tissue growth as deep as the pelvis of the kidney. In these regions, of which there are several, extensive destruction of the glomeruli and the tubules has occurred. Hyaline and granular material fills the tubules, the tubular epithelium being represented in many cases by a shrunken nucleus and a slender layer of cell bodies. The fibrous tissue is organized and dense, and what vessels have originally taken part in the active process of repair are now sharing in construction and obliteration, as in scar tissue. The kidney presents all stages of advanced productive nephritis, apparently as the direct result of the coagulation infarct which must have resulted at the time of the injection of alcohol into the kidney substance.

PROTOCOL 7.

Dog.—White and black fox terrier, female; weight after three months' probation period 9850 G. Urine, free from albumin and casts, specific gravity 1024. From Feb. 2 to Feb. 27, 1906, the dog received ten injections into the left kidney of 6 c.c. each of 25 per cent. alcohol.

Dec. 20, 1906: Weight 6300 G.; the dog has been failing for past four weeks, appetite is poor and diarrhea is present, lately increasing to general convulsive seizures.

Dec. 24, 1906: Died. Weight 6000 G.

Autopsy.—Lungs show hypostatic congestion at the bases; the heart and vessels appear normal; right kidney normal; left kidney adherent to lateral abdominal wall; kidney substance appears normal.

Histologic Examination.—Heart and liver show no variations from normal. Right kidney appears normal. Left kidney shows moderately thickened capsule and a few areas of connective tissue infiltration from the capsule inwards. There is no degeneration or inflammatory process throughout the kidney parenchyma.

ADRENALIN.

Adrenalin was used in one dog in the expectation that some distinct difference between the resulting constriction of vessels locally and the effect of alcohol on the kidney might appear.

PROTOCOL 8.

Dog.—White female mongrel; weight 7150 G. No albumin or casts found after four months' probation period. Between Jan. 11, 1906, and Feb. 27, 1906, nineteen injections of 3 c.c. each of adrenalin chlorid solution (1 to 1000) were given into the left kidney.

April 18, 1906: The dog died suddenly without having been ill so far as could be observed. Weight 8200 G.

Autopsy.—The skin and mucous membranes were very pale, the viscera were deeply colored, but apparently not congested. The heart appeared enlarged and distended with dark venous blood. A small amount of pericardial fluid was found. The lungs were collapsed and congested.

Histologic Examination.—The two kidneys appear the same except for the lesions made by the needle in the left kidney; its parenchyma and capsule show injury. In both kidneys the capsule, glomeruli and tubules are normal except in the immediate vicinity of the lesions just noted. The lumen of the tubules appears empty or containing a small amount of cell detritus. The heart, aorta, liver and lungs are normal.

SODIUM CHLORID.

Normal salt solution, 0.8 per cent., was used as a control to see what effect on the kidney the injection of an isotonic non-toxic solution would have.

PROTOCOL 9.

Dog.—Black and white female fox terrier. Weight 8180 G.; no albumin or casts in urine after four months of probation period; specific gravity 1020.

Between Jan. 11 and Feb. 27, 1906, nineteen injections of normal salt solution of 6 c.c. each were given into the left kidney.

March 24, 1906: In fine condition, no albumin.

Feb. 25, 1907: Weight 9800 G.; in fine condition, no albumin.

July 19, 1907: Killed by destroying the medulla by pithing. Weight 7940 G.; active and alert though thin.

Autopsy.—Left kidney showed an area of thickened capsule where it was adherent and contracted. Right kidney and the other organs are normal.

Histologic Examination.—The heart, aorta, liver, and right kidney present wholly normal structure. The left kidney shows much thickened capsule with areas of newly forming connective tissue in the cortex and as deep as the medullary portion, obliterating the tubules and resembling the wedges of productive connective tissue resulting from decapsulation of the normal kidney, or the kidney in chronic nephritis, with the exception that the areas in the kidney under consideration are long, narrow and confined within pretty distinct limits, suggesting strongly that these areas represent the scar tracts left by the penetrating needle.

MECHANICAL INJURY.

Two dogs were used to test the effect of the mechanical injury of inserting a hypodermic needle in the renal parenchyma.

PROTOCOL 10.

Dog.—White and brown female terrier, weight 6130 G.; at the end of a two-months' probation period. No albumin or casts.

Between Jan. 11 and 31, 1906, the hypodermic needle was passed into the left kidney nine times.

January 31: Being in doubt as to the accuracy of my manipulation of the needle, the dog was lightly chloroformed with the intention of locating the needle more exactly in the kidney. Unfortunately the dog died under the narcotic, but the needle was found to have been placed directly into the kidney.

Autopsy.—Nothing abnormal was found except a few recent hemorrhagic areas in and beneath the kidney capsule.

Histologic Examination.—No variations from normal were found except slender tracts of young connective tissue in the left kidney.

PROTOCOL 11.

Dog.—Yellow mongrel female. After three months of probation period, weight 6550 G.; no albumin or casts.

Between Feb. 1, and 27, 1906, the left kidney was needled twelve times.

Feb. 14, 1907: After a period of severe mange accompanied by diarrhea and loss of weight to 3600 G. the dog died.

Autopsy.—No macroscopic changes noted except total absence of fat throughout the body; kidneys showed no gross lesions.

Histologic Examinations.—The liver specimen was excessively hardened and could not be sectioned. The heart muscle and aorta appear normal. The lungs show congestion and in a few small areas, the alveoli are filled with blood though not presenting the appearances of inflammatory consolidation. The left kidney shows a thickened capsule with dense connective tissue pressing irregularly on the cortex and in places invading it. There is new connective tissue formation in several narrow areas deep in the parenchyma of the kidney, presumably the lines of needle puncture. Except for these evidences of injury there is no appearance of nephritis, the glomeruli and tubules appearing normal.

SUMMARY B.

1. Injections of alcohol into the kidney substance cause connective tissue increase in the kidney, resulting in an interference with the nour-

ishment of the tubules and the glomeruli, which resembles the milder grades of chronic productive nephritis.

2. Adrenalin injected into the kidney substance is not of itself the cause of any circulatory or inflammatory changes locally, although the injury incident to injection shows a resulting scar.

3. The use of the hypodermic needle without any injection fluid, and the use of normal saline injections into the kidney substance, are both followed by the formation of connective tissue tracts in the kidney which resembles the replacement fibrosis which occurs in chronic nephritis. That is, the structural changes observed in nephritis in man is imitated, but there is no general distribution of the connective tissue throughout the kidney such as appears when there is a true inflammatory process.

*C. EFFECT ON THE KIDNEY OF INCREASED VISCOSITY OF THE BLOOD
DUE TO THE ADDITION OF GELATIN TO THE BLOOD STREAM;
AND OF SOLUTIONS OF ADRENALIN CHLORID
AND OF ACETATE OF LEAD.*

GELATIN.

In spite of the fact that increased viscosity as a possible cause of renal disease has been examined and found wanting by Hirsch and Beck,⁷ it seemed possible that if gelatin were added to the blood over a period of days some circulatory or structural changes might be found in the kidney. Opitz⁸ has found that gelatin solutions increase the viscosity of dog's blood promptly and to a considerable degree.

PROTOCOL 12.

Dog.—Black and white mongrel male, weight 10000 G. After three months' probation period; no albumin or casts in urine; specific gravity 1048.

Between Jan. 18 and Feb. 27, 1906, nineteen injections of 5 per cent. gelatin in water of 6 c.c. were given into one of the superficial veins of the dog's legs.

No albumin or casts were found at any time in the urine of this dog, and on July 19, 1907, he was killed by "pithing." In fine condition, weight 9320 G.

Autopsy and histologic examination revealed no variations from normal in any tissue.

ADRENALIN CHLORID.

The use of repeated doses of adrenalin chlorid in the general circulation causes temporary vasoconstriction in all the vessels of the body except those of the lungs, a great contraction of the kidney vessels and a temporary decrease in the secretion of urine. This is a matter of common laboratory observation and has been made the subject of exact record recently published by Schlayer and Hedinger.⁹ Such a phenomenon,

7. Hirsch and Beck: *Deutsch. Arch. f. klin. Med.*, 1902, lxii, 560.

8. Opitz: *Arch. f. d. ges. Physiol.*, 1900, lxxxii, 447.

if repeated, might be expected to cause some permanent alteration in the blood supply, function or structure of the kidney.

PROTOCOL 13.

Dog.—Unfortunately the dog used for this test was infected after seventeen injections of 3 c.c. each of adrenalin chlorid solution, and death resulted from pyemia a few days later.

Histologic Examination.—The histologic picture of the kidneys was that of acute degeneration with hemorrhages in the parenchyma. No conclusions could be drawn from this test and time was lacking to repeat it.

ACETATE OF LEAD.

As a control test to have some recognized type of experimentally produced nephritis to compare with the lesions produced by the other procedures used in this study, the intermuscular injection of solutions of acetate of lead was adopted.

PROTOCOL 14.

Dog.—Feb. 22, 1906: White and black terrier, male, weight 9850 G. After three months' probation period the urine showed no albumin or casts. Over a period of two months injections of 1 c.c. each of a 10 per cent. solution of acetate of lead were given in the muscles of the legs.

August 14, 1906. For the past two weeks, convulsions and considerable loss of weight.

Autopsy.—Except for the smallness and hardness of the kidneys no variations from normal were found.

Histologic Examination.—The heart muscle shows no abnormal structure. The section of the aorta shows no thickness of the elastic coat, no separation of the elastic fibers and no infiltration or degeneration of the endothelial coat. The vasa vasorum appear healthy. The liver appears normal. The kidneys show no change in the capsule as to their thickness or vascular supply. The glomeruli are distended, everywhere filling the capsule of Bowman completely. The tufts appear to be the seat of active cell proliferation. The capsular cells are not increased. There is no atrophy, but a uniform swelling of the glomerular tufts. The tubular epithelium fills the lumina almost everywhere. There is little cellular detritus in the tubules. The cells lining the straight and convoluting tubules are swollen. There are occasional hemorrhages among the tubules, in some of which absorption is in process; others are evidently recent. The condition resembles that of a mild chronic degeneration more than a chronic productive nephritis which would probably result if the poisoning had been more severe or the period of observation longer.

SUMMARY C.

1. Increased viscosity of the blood due to the presence of gelatin does not affect the kidneys.
2. Lead acetate solution caused a chronic degeneration of the kidneys.
3. Although the test with adrenalin was inconclusive, this failure is not of vital importance, as Loeb¹⁰ found that inflammatory processes

9. Schlayer and Hedinger: *Deutsch. Arch. f. klin. Med.*, 1907, xc, 1.

10. Loeb: *Am. Jour. Med. Sc.*, 195, cxxx, 665.

never resulted from adrenalin injections, the effect being degeneration processes in various stages.

DISCUSSION.

The function of the healthy kidney depends on three main classes of factors. Of paramount importance is the blood flow through the kidney, which may vary in its pressure, its rate, and the size of the vascular path to and from the glomeruli and the convoluted tubules. The quality of the blood reaching the kidney is important, as it has been shown to affect renal secretion through variations in its chemical composition, its temperature, its viscosity, and its osmotic pressure. Direct and reflex nervous stimulation also has been shown to alter the activity of the renal epithelium.

When we find errors in the function of the kidney we must look to some alteration of the normal nerve control, or to some defect in the quality of the blood, or to some error in the character of the circulation. Even grave defects of function may exist and persist even for long periods, as, for example, the excessive diuresis in diabetes insipidus, without necessarily being accompanied by any appreciable alteration in the secreting cells or in the blood vessels of the kidney.

Very considerable alteration of the kidney structure is frequently found without any suspicion having been aroused of faulty function of the kidney, either by the general health of the individual before death, or by exact analysis of the urine. It is apparent, then, that the experimental study of chronic diseases of the kidney can not be expected to give a full answer to the question of etiology.

Histologic examination of kidneys often reveals advanced structural changes which have not been suspected by a faulty function during life.

Urinary analysis fails to supply an altogether reliable source of information as to changes of renal structure, and still less in regard to temporary errors in the function. Blood analysis, as by cryoscopy, supplements our other means of diagnosis, but is not invariably sufficient to point to the exact character or degree of renal disease.

Delafield¹¹ tersely states: "Any educated physician will now admit that albumin may be absent with kidney disease and present without it."

A recent test, applied by Schur and Weisel,¹² which, it is claimed, will detect the presence in the blood of nephritics of a substance exerting the mydriatic effect of adrenalin on the frog's eye, may add to our means

11. Delafield: *Lectures on the Practice of Medicine*, New York, Part I, 8-17; Part IV, 412-496.

12. Schur and Weisel: *Wien. klin. Wchnschr.*, 1907, xx, 699.

of diagnosis. They say that the sera of normal people do not give this reaction.

We may expect as much information from the accumulation of clinical data as from animal experimentation.

A summary of the procedures which have been adopted in animal experimentation shows only a few which have actually resulted in the approximation of lesions such as are found in chronic nephritis in man. Ophüls¹³ considers that Ehrlich¹⁴ and Levaditi¹⁵ have produced chronic nephritis by the use of vinylamin. Paessler and Heineke¹⁶ obtained chronic nephritis by operative removal of large parts of the kidney substance. Posner¹⁷ quotes Orth as having obtained nephritis in rabbits by subcutaneous bruising of the kidney. Similar lesions have been produced in the present study by coagulation infarcts due to the injection of alcohol into the kidneys. These lesions, due to operative removal, chemical or mechanical injury, and subsequent fibrous repair, are all similar to the cases of chronic productive nephritis reported in the experimental results of Johnson,¹⁸ Emerson,¹⁹ and Osmoloffski²⁰ after decapsulation of the kidney in animals.

Among the means which have been used to cause the production of interstitial changes in the kidney are aloin, boracic acid, cantharidin,^{21,9} potassium chlorate, chromic acid, potassium bichromate,²² salts of lead,¹³ mercury⁹ and arsenic,⁹ oxalic acid, oxamid, sulphuric acid, the toxins of the pneumococcus and of the diphtheria bacillus,⁹ uranium nitrate, theocin,^{20, 23} excessive amounts of chlorids²⁴ and phosphates,²⁵ alcohol²⁶ and nephrotoxic serum.³

Caro²⁷ found nephritis in cats from five to eight days after experimental removal of the thyroid.

Of all these procedures, the use of small doses of the salts of lead is

13. Ophüls: Jour. Am. Med. Assn., 1907, xlviii, 483.

14. Ehrlich: Internat. Beitr. z. inn. Med., 1902, i, 647.

15. Levaditi: Arch. internat. de pharmacod., 1901, viii, 45.

16. Paessler and Heineke: Verhandl. d. deutsch. path. Gesellsch., Berlin, 1905, p. 99.

17. Posner: München. med. Wehnschr., 1906, liii, 531.

18. Johnson, H. A.: Ann. Surg., Philadelphia, 1903, xxxvii, 592-601.

19. Emerson, H.: Am. Jour. Med. Sc., 1904, p. 692.

20. Osmoloffski: Russk. Vrach, 1903, ii, 801.

21. Brodzki: Berl. klin. Wehnschr., 1906, xliii, 906.

22. Blank: Ztschr. f. klin. Med., Berlin, 1906, lx, 400.

23. Heineke and Myerstein: Deutsch. Arch. f. klin. Med., 1907, xc, 101.

24. Weber: Arch. f. exper. Path. u. Pharmakol., 1905-6, liv, 1.

25. Leopold: Ztschr. f. klin. Med., 1906, lx, 481.

26. Friedenwald: Jour. Am. Med. Assn., 1905, xlv, 780.

27. Caro: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1907, xvii, 447.

the only one which is known to produce regularly a chronic nephritis in man and animals. All the other procedures have resulted in degeneration of the kidney of an acute or chronic character, or have caused but temporary lesions which leave no permanent effect on the kidney parenchyma.

We have, then, two methods which caused what resemble the lesions, but not the clinical picture of chronic nephritis in man: the use of lead salts and the formation of scar tissue within or on the surface of the kidney. It is true that neither of these can be considered as frequent causes of nephritis in man.

The causes usually included in the etiology of chronic nephritis in man come under four headings:

1. Infectious diseases: scarlet fever, diphtheria, pneumonia, typhoid fever, tuberculosis of any part of the body, septicemia, and erysipelas.
2. The poisons of gout, rheumatism, syphilis, and lead.
3. Vices of appetite; the excessive use of nitrogenous and other stimulating foods and drinks.
4. Errors persistent, or frequently repeated, in the circulation; cardiac disease; exposure to wet and cold; muscular fatigue; attacks of acute or chronic congestion and degeneration of the kidney; attacks of acute exudative nephritis; mental worry and anxiety.

Loeb²⁸ would add that non-nephritic albuminuria leads in a high percentage of cases to a real nephritis, and his reasoning to this end is important. He finds that orthostatic albuminuria is, in a majority of cases, of cardiovascular origin. A diminished blood flow through the kidney with increased pressure in the renal vein is the cause of renal hyperemia. This condition is often due, according to Krehl,²⁹ to the "cor juvenum."

Again, J. Rose Bradford,³⁰ although denying that all cases of orthostatic albuminuria lead to a chronic lesion, explains the increase of albuminuria in a convalescent from acute nephritis when assuming the erect posture, by the less advantageous circulation which the kidney obtains in this position.

Delafield³¹ gives cases to show that albuminuria appears after prolonged exertion owing to a congestion of the kidneys. After cessation of the exertion the albumin regularly disappears within a few hours.

28. Loeb: *Deutsch. Arch. f. klin. Med.*, 1905, lxxv, 348; lxxxiii, 452.

29. Krehl: *Deutsch. med. Wehnschr.*, 1905, xxxi, 1872; *Deutsch. Arch. f. klin. Med.*, 1906-7, lxxxviii, 351.

30. Bradford: *Brit. Med. Jour.*, 1907, i, 725.

Fothergill³¹ (1887) states that the knowledge of that time warranted the conclusion that "the waste-laden condition of the blood causes a contraction of the tiny arterioles producing high tension. The sustained high arterial tension sets up atheromatous changes in the arterial walls, and from this spring a number of maladies." While this idea has much to support it and has been widely accepted up to the present time, the studies of Slade,³² of Sollmann³³ and of Opitz⁸ suggest that this conception is wrong, and that in the case of meat extractives, although there is a general contraction of all smooth muscle tissue, a vasodilatation of the kidney vessels occurs.

Slade found that: (1) Muscle extracts increased the rate and activity of the heart. (2) Blood vessels are constricted. (3) Plain muscle of the whole body shows increased movement. (4) In the form of beef tea, moderate diuresis accompanied by vasodilatation of the kidney occurs.

Sollmann finds that if the viscosity of the blood is increased a dilatation of the renal arteries and veins occurs in the perfused excised kidney, and that blood has a dilator effect on the vessels of the excised kidney.

Opitz finds that a heavy meat diet materially increases the viscosity of the blood in dogs.

It would be easier to accommodate this series of experimental results in a theory which postulated a dilatation of the kidney vessels at a time when the other vessels of the body are contracted, rather than in any supposition which demands that the kidney must share uniformly in the contraction of the blood vessels of the body at large. When there is an increase in proteid extractives in the blood, the viscosity of the blood is increased, and if these substances remained in the body they would do harm. The stimulus of these harmful substances is apparently responded to by two circulatory changes, a constriction in the vessels of the body at large, causing high blood pressure, and a dilatation of the vessels of the kidney. These alterations in the circulatory distribution would at once put the kidney in the best possible condition to secrete, i. e., a wide capillary path and high general blood pressure, providing a maximum amount to pass through the kidney in a given time.

That there is a general vasoconstriction and general rise of blood pressure is a common observation in nephritis, but it can not at all be claimed that constriction of the renal vessel occurs coincidently, and it is

31. Fothergill: Vaso-renal Changes versus Bright's Disease, New York, Putnam, 1887.

32. Slade: Jour. Physiol., 1907, xxxv, 165.

33. Sollmann: Am. Jour. Physiol., 1905, xiii, 24.

to be noted particularly that the splanchnic blood vessels do not necessarily exhibit vasomotor changes identical with those of the skin and muscles. The effect of cold on the surface of the body is to contract the vessels of the skin, and this is usually accompanied by diuresis, as Dubois and Butruille³⁴ have recently demonstrated so successfully, and in this case the increased activity of the kidney must be supposed to be due to the presence of more blood in the kidney, which can not itself be directly affected by the cold which constricts the vessels of the surface of the body.

As Graupner³⁵ says, high blood pressure occurs in nephritis as soon as substances are retained that should be excreted, and it drops spontaneously as soon as the renal function is re-established. Or it may be said that an increase in the substances to be excreted puts more work on the normal kidney. Increased function demands increased blood flow. This is accomplished under physiologic conditions by a rise in blood pressure due to increased heart action and vasoconstriction, and we may suppose to a dilatation of the renal vessels, although a positive proof of this is not at hand.

Morse³⁶ thinks that a certain proportion of cases of chronic nephritis in man may be due to the action of chemical substances produced by bacteria, inasmuch as the human kidney is more or less constantly exposed to the action of such substances.

Grund³⁷ finds that cystoscopy, ureteral catheterization, and stone in the bladder cause reflex interference with renal functions to such a degree as to lead to grave errors in the functional powers of the kidney, as well as to difficulties in drawing reliable conclusions from urinary analysis under such conditions.

Carter,³⁸ in a critical and experimental study of the etiology of nephritis in Galveston, Texas, concludes that the excessive use of meats in a warm climate and carelessness in recognizing and treating infectious diseases, and not the climate *per se*, are responsible for the prevalence of kidney disease in that region.

v. Homeyer,³⁹ in a study of nephritis in the German army from 1884 to 1904, found the commonest cause of acute nephritis to be the infectious diseases scarlet fever, tuberculosis and diphtheria. Second in fre-

34. Dubois and Butruille: *Echo méd. du nord*, 1907, xi, 253-255.

35. Graupner: *Berl. klin. Wehnschr.*, 1907, xlv, 453.

36. Morse: *Jour. Exper. Med.*, 1896, i, 613.

37. Grund: *München. med. Wehnschr.*, 1906, lxii, 1803.

38. Carter: *Med. News*, New York, 1904, lxxxv, 919.

39. Homeyer: *Ueber die Häufigkeit der Nierenkrankheiten in der deutschen Armee 1884-1904*, Inaug. Diss., Munich, 1907.

quency as a cause of acute nephritis he found to be chilling and wetting of the body, as by sleeping on the damp ground. He found that chronic nephritis was often traceable to chilling, and excessive bodily exertion to the degree of fatigue, especially in men who had passed through an acute nephritis at an earlier date.

Delafield says,⁴¹ "As soon as the blood accumulates in the veins to any considerable extent, the kidneys suffer. One of three things regularly happens to them: either a chronic congestion, chronic degeneration or chronic nephritis is developed." And, again: "The same mechanical obstructions to the circulation—heart disease, pleuritic effusions, etc.—which produce chronic congestion can, instead of this, produce chronic degeneration."

It must be apparent that Councilman's⁴⁰ conclusion is correct: that kidney disease is not an entity, but that the kidney is secondarily affected.

If we examine the causes of nephritis as they have been outlined in the four classes above, it will be noticed, I think, that there is one important factor either constituting the entire cause, as commonly accepted, or playing an important part, if not an usually accepted part, in each instance. I have reference to circulatory stagnation in the kidney. In the infectious diseases the exact physiologic effect of the several bacterial toxins has not been completely studied. We have enough clinical data, however, to supplement the few experimental results that are available.

The work of Paessler and Romberg⁴¹ showed that the cause of death in diphtheria and in experimentally produced pneumonia was due, not to cardiac failure, but to a toxic paralysis of the peripheral or central vasomotor control, resulting in vascular stasis.

In typhoid fever⁴² and tuberculosis^{43, 44, 45} low blood pressure exists for long periods, and there is some experimental proof that the toxins of the tubercle bacillus, at least, have a marked vasodepressor action.

In streptococcus infections, as septicemia, erysipelas, and we might almost say in scarlet fever, the uncomplicated results on the circulation

40. Councilman: Jour. Am. Med. Assn., 1906, xlii, 81.

41. Romberg and Paessler: Arch. f. exper. Path. u. Pharmacol., 1899, xlii, 283.

42. Janeway, T. C.: Am. Jour. Med. Sc., 1907, cxxxiii, 50.

43. Regnault: Le cœur chez les tuberculeux, Paris, 1899.

44. Arloing, Rhodet and Courmont: Cong. p. l'étude de la tuberculose, Paris, 1891, ii, 29.

45. Charrin and LeNoir: Compt. rend. Soc. de biol., Paris, 1893, v, series 9, p. 769.

are those of low blood pressure, the pressure not rising in scarlet fever until albuminuria is established.

In nephritis following gout, rheumatism, syphilis and chronic lead poisoning, the case is not so clear, but it must be kept in mind that in all four of these instances there is a marked tendency to fibrous tissue formation, especially in the walls of the blood vessels. The high blood pressure which results from chronic arteritis may be preceded by stages of insufficient pressure which we fail to recognize clinically.

Where we are considering what I have called vices of appetite or habit it will be noticed that the substances mentioned are all classed commonly as stimulants, in that they produce temporary increase in cerebral activity. Excess of activity is compensated for physiologically by relaxation and rest, and I believe that it is not too much to claim that in all instances where abundant use of meat and stimulants is indulged in the circulation undergoes considerable depression after the immediate effect of the increased activity has passed. The dilated facial capillaries of the hearty eater and drinker are an evidence of vascular stasis following frequently repeated over-stimulation.

What I believe can be shown to be the entire cause of chronic nephritis in many cases is the result of the various disturbances included in the last group. Exposure to wet and cold cause a central congestion by peripheral constriction in the skin and muscles. Muscular exertion, if carried to the degree of fatigue, results in general relaxation of vascular tone. Previous attacks of acute exudative, acute congestive and acute degenerative nephritis leave the kidney especially susceptible to subsequent congestion, and are, if repeated, sufficient cause for persistent congestion and nephritis. The pale surface and tightened artery of the man under the strain of business or professional cares is familiar, and every such picture presents an instance of physiologic fatigue, in which the vasomotor center is being excessively stimulated and the heart is pumping against unnecessarily high resistance. The result is visceral congestion.

Congestion causes functional inadequacy in any tissue. Inadequacy of renal function causes, among other things, according to Leopold,²⁴ a retention of chlorids and phosphates in the blood, and the presence of an excess of chlorids and phosphates in the blood may cause albuminuria, which of itself is a sign of faulty function and faulty circulation.

The improvement in chronic nephritis under such treatment as is directed chiefly to maintaining the circulation at a constant level of efficiency is an indication that circulatory error probably shared in the

causation of the disease. Webster's⁴⁶ summary of the treatment of chronic nephritis may properly be taken as a type of treatment that would be generally accepted. He advises dietetic moderation beyond the point of supplying ample food to carry on bodily functions and maintain nutrition; woolen clothing, bathing, open-air life where there are no rigors of climate; exercise never to the point of fatigue, to maintain the cardiovascular equilibrium at its most efficient point.

The suggestions with which Janeway⁴² supplements Loeb's²⁷ theory of the causation of increased arterial tension and cardiac hypertrophy in chronic nephritis show a similar conviction to the one I have expressed.

"In chronic kidney disease we must look for some cause of the increased pressure. May it not be that the conditions of the circulation in the kidney are such that an increased pressure must be maintained in order to accomplish the necessary amount of secretion? Any local or general cause of slow blood flow, or low blood pressure, or congestion or stagnation in the renal circulation would at once be met by an increase in general blood pressure. If this is continually persisted in, it is entirely conceivable that it might become permanent. Increased arterial pressure is a symptom, or, more truly, a proof of the body's defensive action against disease."

Or as Loeb himself says: "Cardiac hypertrophy and increased blood pressure are compensatory reactions, occurring when the glomeruli are imperfectly supplied with blood, because inflammation or stasis has allowed too low a capillary pressure for proper filtration."

Schlayer and Hedinger⁹ note that every injury to the renal vessels resulting in an error of circulation expresses itself in a diminution of diuresis.

CONCLUSIONS.

From experimental results it would appear that interference with the blood supply of the kidney can be accomplished by means of chemical injury to the renal parenchyma, and that the process of repair which ensues may involve such a destruction of secreting tissue as to cause the death of the animal.

From the experimental use of general vasodilators, it appears that the kidney suffers at least mild grades of degeneration, which may be due, not to the specific renal irritation of the drugs employed, but to the defective blood supply which frequently repeated vascular relaxation causes.

From an analysis of the accepted causes of chronic nephritis in man it is evident that many of them have as a common factor a more or less

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46. Webster: *Am. Jour. Med. Sc.*, 1907, cxxxiii, 271.

severe and prolonged stagnation in renal blood supply, and, although this factor is often accompanied by the presence of irritants which we recognize as injurious to the kidney tissue, insufficient blood supply alone will cause, first, an error in the function and later an alteration in the structure of the kidney.

As convincing proof of the true cause or causes of chronic nephritis in man is not present, we must perforce accept as a theory one which will account for most of the known facts. Loeb's explanation of the probable sequence of the circulatory events coincident with the course of chronic nephritis in man might reasonably be supplemented by an explanation of the etiology of nephritis which recognizes as a frequent, if not an invariable factor, deficient renal circulation. Faulty function always results from deficiencies of blood supply and if the defects persist or are frequently repeated faulty structure results. In the case of the kidney, the fault in its function resulting from the altered structure in chronic nephritis will cause much or little disturbance in the body at large according to the degree of circulatory compensation which can be maintained. Cardiac disease, bacterial toxins, and metabolic waste products are probably the causes of the errors in circulation which cause, first, faulty function in the kidney and, finally, chronic nephritis.

If this theory of etiology is supported by subsequent study, its application to the prevention of nephritis might strengthen existing efforts to check the spread of infectious disease, and to urge moderation in the habits of over-stimulation and over-work, which are prominent in present day life in large centers of population.⁴⁷

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47. In addition to the above, the following references will be found of interest: Barr: *Brit. Med. Jour.*, 1907, i, 725. Georgopoulos: *Ztschr. f. klin. Med.*, Berlin, 1906, lx, 411. Josué: *Presse méd.*, 1907, xv, 233. Lutheus: *Arch. f. exper. Path. u. Pharmacol.*, 1906, lv, 116. Paessler: *Samml. klin. Vortr.*, 1906, new series, No. 2, p. 408. Paessler and Rolly: *Deutsch. Arch. f. klin. Med.*, 1903, xvi, 217. Riegel: *Ztschr. f. klin. Med.*, Berlin, 1884, vii, 260. Thayer: *Am. Jour. Med. Sc.*, 1904, lxxvii, 391.