THE STABILITY OF THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN NATURALLY NEPHROTIC ANIMALS AND THE EFFECT ON RENAL FUNCTION OF CHANGES IN THIS EQUILIBRIUM.

I. A STUDY OF THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN NATURALLY NEPHROTIC ANIMALS AND OF THE FUNCTIONAL CAPACITY OF THE KIDNEY IN SUCH ANIMALS FOLLOWING AN ANESTHETIC.*

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Plates 49 and 50.

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As a result of the observations of Ophüls,\(^1\) Pearce,\(^2\) and Dayton,\(^3\) the fact is generally known that many of the lower animals, particularly the dog, are susceptible to a type of kidney injury which should be classed as a chronic nephropathy. In a recent study\(^4\) of the naturally acquired chronic nephropathy of the dog these earlier observations have been confirmed, the various nephropathic processes have been classified, and a consideration of the processes of repair in the kidneys has been undertaken. In this study of forty-two naturally nephropathic animals I found it possible, with three exceptions, to classify the kidney injury as a chronic productive type. The three remaining animals showed the typical arteriosclerotic type of kidney with extensive general sclerosis of the vessels. The thoracic aorta in one of the animals was the seat of a fusiform aneurysm. In the majority of kidneys of the remaining thirty-nine animals the

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formation of connective tissue was a focal process confined to the glomeruli. In all the animals both the capsule and capillaries of the glomeruli participated in the laying down of connective tissue so that in the different animals it was not possible to specialize the glomerular pathology into a capsular and intracapillary glomerulonephropathy. Hyaline degeneration of the fibrosed capillary tufts was occasionally observed.

The formation of intertubular connective tissue in the kidneys of these animals has shown no parallel with the degree of fibrosis which has taken place in the glomeruli, and, furthermore, there has existed a notable disproportion between the severity of the changes in the glomeruli and the degree of degeneration of the tubular epithelium. This observation has been recently confirmed by Stengel, Austin, and Jonas in a study of the chronic nephropathies in human material.

The above outline of the naturally acquired chronic nephropathy of the dog not only establishes the frequency of the occurrence of such conditions in these animals but shows the close histological resemblance between certain nephropathies of the lower animals and man. The ability to obtain such material for experimental purposes offers many possibilities for the study of the chronic nephropathies and for the study of various acute processes which may be superimposed upon the naturally acquired chronic kidney injury.

The first study of this character has consisted in an investigation of the functional response of the naturally nephropathic kidney after the kidney had been acutely injured by uranium nitrate or by an anesthetic. An analysis of these experiments shows that when a naturally nephropathic animal is anesthetized by Gréhant's anesthetic, or when the animal is given uranium and anesthetized by ether, the animals fall into two clearly defined groups. One group of animals during the anesthesia becomes rapidly anuric and fails to show a functional response to such diuretic substances as theobromine, caffeine, and solutions of urea and glucose. The second group of animals remains diuretic following the anesthetic and shows a functional response to the diuretic substances which in the first group of animals were of no diuretic value.

A physiological study of the response of the vascular mechanism of the kidney in the anuric and diuretic groups of animals by the use of such peripherally acting stimuli as the members of the caffeine group and adrenalin has shown this

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mechanism to be responsive in both groups of animals. The degree of vasodilation or constriction of the renal vessels induced by caffeine or adrenalin was usually greater in the anuric than in the diuretic groups of animals. Renal vasodilation effected by caffeine, theobromine, or solutions of urea or glucose in the diuretic group of animals was associated with a free diuresis, while with the production of an even greater degree of vasodilation by these substances in the anuric animals no formation of urine was induced.

The histological study of the kidneys of these two groups of animals has shown a chronic productive nephropathy in which the changes were largely confined to the glomeruli. As a result of the use of uranium or an anesthetic no acute degenerative changes had developed in the glomeruli. The vascular pathology in the two groups has shown no elements of difference. The acutely developing pathological change which differentiates the anuric from the diuretic groups of animals has consisted in the degree of degeneration occurring in the tubular epithelium, and especially in the epithelium of the convoluted tubules. The animals which have remained diuretic and responsive to diuretic substances have shown but slight epithelial damage, while the group of animals that have been rendered anuric by the anesthetic and non-responsive to the same diuretic substances have shown a swelling and necrosis of the convoluted tubule epithelium. The ascending limbs of Henle's loops have contained a large amount of stainable fat.

The following investigation has been undertaken with the object in view of ascertaining the difference in the response of the normal and naturally nephropathic kidney to Gréhant's anesthetic, the principal anesthetic ingredient of which is chloroform. The study embraces an investigation of the acid-base equilibrium of the blood in these two groups of animals, prior to and during the period of anesthesia, and the association of the changes in this equilibrium with the development of an anuria. The functional capacity of the kidney has been determined by the phenolsulfonephthalein test, the retention of blood urea, and the response of the kidney during the period of anesthesia to various diuretic substances. Finally, the relative toxicity of this anesthetic for the normal as compared with the naturally nephropathic kidney has been investigated by a histological study of the kidneys at the termination of the experiments.
EXPERIMENTAL.

Dogs were employed in the experiments which furnish the basis for this study. Nine of the animals were healthy dogs varying in age from 8 months to 6 years and 2 months. Eighteen of the dogs were naturally nephropathic and varied in age from 3 years to 13 years and 1 month. Both the normal animals which served as controls and the naturally nephropathic animals were placed in metabolism cages, given 500 cc. of water daily, and fed on bread with a small amount of cooked meat. The animals were studied for 3 days prior to the day of experiment. During this period the urine was collected twice a day and examined qualitatively for albumin, glucose, acetone, and diacetic acid. Quantitative determinations of these substances were made when present. The centrifugalized urine was examined for casts. The hydrogen ion content of the blood was determined by the method of Levy, Rowntree, and Marriott,\(^7\) the alkali reserve of the blood and the tension of carbon dioxide in alveolar air by the methods of Marriott,\(^8,9\) while the blood urea was determined by the method of Marshall\(^10\) as modified by Van Slyke and Cullen.\(^11\) The phenolsulfonephthalein test for kidney function was conducted according to the technique of Rowntree and Geraghty.\(^12\)

At the end of the 3 day period allowed for normal observations the animals were given 300 cc. of water and 3 hours later were given 60 cc. per kilo of Gréhan's anesthetic by stomach tube. Half an hour was allowed for the development of a degree of anesthesia sufficient for


the surgical part of the experiment. The first observations were made on the anesthetized animals 1 hour after they had received the anesthetic and half an hour after the development of a satisfactory state of general anesthesia. At half hour periods during the course of the experiments the flow of urine per minute was recorded and the hydrogen ion content and reserve alkali of the blood were determined. At these intervals the animals were given intravenously one of the following diuretic substances: caffeine citrate or theobromine sodium salicylate in 1 per cent solution, 1 cc. per kilo; pituitrin (Parke, Davis and Company) 0.5 cc.; or solutions of urea or glucose. The urea solution was of 0.9 per cent strength in 0.9 per cent sodium chloride and was given in the quantity of 10 cc. per kilo. The glucose solution was 20 per cent strength in 0.9 per cent sodium chloride and was given in the same quantity per kilo as was the urea solution.

The experiments on the anesthetized animals were terminated at the end of 1½ hours at which time the tension of carbon dioxide in alveolar air was determined and the kidneys were removed for the histological study.

Observations on Normal and Naturally Nephropathic Animals Prior to an Anesthetic.

The following observations which have extended over a period of 3 days have been recorded in Table I. In this table observations on two normal or control animals have been tabulated with similar observations on nine of the naturally nephropathic animals.

In recent papers13,14 studies have been made of the relative stability of the acid-base equilibrium of the blood in animals of different ages. In these studies it was found that the older animals were more susceptible to agents which altered this equilibrium in favor of the acid ion than were the younger animals. For this reason relatively young animals were selected for the controls in these experiments. The factor of the age of the animal as expressed by the ease with which

13 MacNider, A consideration of the relative toxicity of uranium nitrate for animals of different ages. I, J. Exp. Med., 1917, xxvi, 1.
14 MacNider, Concerning the influence of the age of an organism in maintaining its acid-base equilibrium, Science, 1917, xlvi, 643.
the nephropathic animals develop an acid intoxication cannot be accurately determined in these experiments, since the existence of the chronic nephropathy in the animals, as will be demonstrated later in this study, makes them more susceptible to changes in the acid-base equilibrium. The naturally nephropathic animals have, however, been arranged in the table according to their age. The influence of this factor in determining the toxicity of the anesthetic will be referred to in a later part of this paper.

Reference to Table I shows the control animals to be freely diuretic and the urine to be free from albumin, glucose, acetone bodies, and casts. The hydrogen ion content of the blood has varied from 7.3 to 7.45, while the reserve alkali has shown a variation from 8 to 8.1. The hydrogen ion determinations by the method employed in these experiments do not show a correlation with the reserve alkali determinations or the determinations of alveolar air carbon dioxide. The Levy-Rowntree-Marriott method is an expression of both the volatile and non-volatile acid content of the blood. Even a local accumulation of carbon dioxide in the blood of a part, such as the arm or leg, may give a very high reading and is not a true expression of the non-volatile acid content of the blood. For this reason the alkali reserve determinations and the variations in alveolar air carbon dioxide tension more accurately indicate the changes in the hydrogen ion content.

The determinations of alveolar air carbon dioxide for the normal animals have varied between 37 and 40 mm. and have shown a correlation with the maximum and minimum variations of the reserve alkali of the blood.

The blood urea estimations have remained very constant. In one of the nine control animals the percentage of urea was 0.014 per cent, while in the remaining animals the blood urea was 0.012 per cent. The phenolsulphonephthalein test was made on six of the control animals. The total output of the dye in a 2 hour period varied from a minimum of 73 per cent to a maximum of 81 per cent.

A study of the observations on the naturally nephropathic animals prior to an anesthetic (Table I) shows a marked variation in the output of urine by the different animals in a 24 hour period. This has varied in the respective animals from 174 to 820 cc. The urine of all the animals contained albumin and casts. In all but two of the animals
### TABLE 1.

Observations on Normal and Naturally Nephropathic Animals Prior to an Anesthetic.

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<td>1 yrs.</td>
<td>8.2</td>
<td>500</td>
<td>481</td>
<td>0</td>
<td></td>
<td>7.3</td>
<td>8.0</td>
<td>37</td>
<td>0.012</td>
<td>81</td>
</tr>
<tr>
<td>(control)</td>
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<td>287</td>
<td>0</td>
<td></td>
<td>7.45</td>
<td>8.1</td>
<td>40</td>
<td>0.012</td>
<td>81</td>
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<tr>
<td>(control)</td>
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<tr>
<td>3</td>
<td>1-2 yrs.</td>
<td>11.3</td>
<td>500</td>
<td>174</td>
<td>Tr. Casts.</td>
<td></td>
<td>7.45</td>
<td>8.15</td>
<td>40</td>
<td>0.015</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>1-2 yrs.</td>
<td>21.55</td>
<td>500</td>
<td>518</td>
<td>&quot; &quot;</td>
<td></td>
<td>7.45</td>
<td>8.1</td>
<td>39</td>
<td>0.018</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>1-2 yrs.</td>
<td>7.32</td>
<td>500</td>
<td>389</td>
<td>1.2 gm. Numerous casts.</td>
<td></td>
<td>7.45</td>
<td>7.9</td>
<td>36</td>
<td>0.018</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>3 yrs. &amp; 4 mos.</td>
<td>11.4</td>
<td>500</td>
<td>584</td>
<td>Tr. Casts.</td>
<td></td>
<td>7.4</td>
<td>8.0</td>
<td>40</td>
<td>0.015</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>17.7</td>
<td>500</td>
<td>820</td>
<td>&quot; &quot;</td>
<td></td>
<td>7.45</td>
<td>8.1</td>
<td>40</td>
<td>0.015</td>
<td>61</td>
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<tr>
<td>8</td>
<td>10</td>
<td>23.1</td>
<td>500</td>
<td>508</td>
<td>&quot; &quot;</td>
<td></td>
<td>7.45</td>
<td>8.0</td>
<td>38</td>
<td>0.015</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>10-11 yrs.</td>
<td>21.55</td>
<td>500</td>
<td>355</td>
<td>&quot; Numerous casts.</td>
<td></td>
<td>7.35</td>
<td>8.0</td>
<td>38</td>
<td>0.015</td>
<td>61</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>23.4</td>
<td>500</td>
<td>718</td>
<td>&quot; Few casts.</td>
<td></td>
<td>7.45</td>
<td>8.0</td>
<td>41</td>
<td>0.015</td>
<td>61</td>
</tr>
<tr>
<td>11</td>
<td>13 yrs. &amp; 1 mo.</td>
<td>30.35</td>
<td>500</td>
<td>520</td>
<td>0.9 gm. Few casts.</td>
<td></td>
<td>7.45</td>
<td>8.1</td>
<td>32</td>
<td>0.028</td>
<td>52</td>
</tr>
</tbody>
</table>
albumin was present as a mere trace. In one animal the urine contained 1.2 gm. of albumin per liter. This animal (Experiment 5, Table I) as contrasted with the other naturally nephropathic animals showed a depletion in the alkali reserve of the blood, a decrease in the tension of alveolar air carbon dioxide, and a marked reduction in the elimination of phenolsulfonephthalein. None of the naturally nephropathic animals of this series has shown the presence of acetone bodies in the urine. The hydrogen ion determinations have been variable as was the case with the control animals. With one exception (Experiment 5, Table I) the alkali reserve of the blood and the tension of alveolar air carbon dioxide in the naturally nephropathic animals have been within the range of normality. The reserve alkali in these animals has varied from 8 to 8.1, while the carbon dioxide tension has varied between 32 and 41 mm. This minimum variation of 32 mm. in carbon dioxide tension does not correlate with the reserve alkali reading for the blood which was 8.1. The question arises as to whether or not some local pathology in the lung of this very old animal could not have been responsible for this atypical reading.

The blood urea determinations have shown a retention in all the naturally nephropathic animals, varying from 0.015 to 0.028 per cent. The elimination of phenolsulfonephthalein has been reduced in all the animals and, as is shown in Table I, there is a relation between the retention of blood urea and the elimination of phenolsulfonephthalein. The animal of Experiment 11, with the greatest retention of blood urea, 0.029 per cent, also shows the greatest reduction in the output of phenolsulfonephthalein which was 52 per cent. The animals with a lower percentage retention of blood urea have a higher percentage elimination of the dye.

From the foregoing analysis of observations on the control and naturally nephropathic animals prior to the use of an anesthetic, the following conclusions are permissible: (1) The control animals show no evidence of a kidney injury and have a normal acid-base equilibrium. (2) The naturally nephropathic animals give evidence of a chronic kidney injury by the formation of a variable amount of urine which contains albumin and casts, by a retention of blood urea, and by a decrease in the elimination of phenolsulfonephthalein. (3) The naturally nephropathic animals with one exception, Experiment 5,
show a normal acid-base equilibrium. (4) In the naturally acquired chronic nephropathy of the dog in which the chronic pathology is largely confined to the glomeruli an acid intoxication is not the primary cause for the kidney injury. (5) In such chronic nephropathies blood urea determinations and estimations of the ability of the kidney to eliminate phenolsulfonephthalein are of more diagnostic value than determinations of the acid-base equilibrium of the blood.

Observations on Normal and Naturally Nephropathic Animals after an Anesthetic.

An analysis of the response of the control animals to Gréhant’s anesthetic as indicated in Table II shows these animals to have remained diuretic following the development of a state of surgical anesthesia. The urine flow varied between 1 and 2 drops per minute for both animals. Half an hour after the establishment of a state of anesthesia the urine flow was unaffected and no change from the normal alkali reserve reading of 8 to 8.1 had occurred. During the remaining hour of the experiment these animals were freely diuretic to theobromine, caffeine, pituitrin, and a solution of glucose. The flow of urine from pituitrin was increased from 5 to 20 drops per minute and an even greater diuretic effect was obtained from the glucose solution, the urine increasing from 5 to 26 drops per minute.

During the course of the experiments the control animals were able to maintain their normal acid-base equilibrium. The alkali reserve of the blood failed to show any depletion and the tension of carbon dioxide in alveolar air remained practically unaffected. At the end of the experiment the control animals were forming a larger amount of urine than was the case at the commencement of the anesthesia. At the commencement of the experiments the urine flow per minute for the animals of Experiments 1 and 2 was 2 and 1 drops for the respective animals, while at the termination of the experiments the urine flow was 3 and 6 drops per minute for these animals.

The histological study of the kidneys of the control animals has been negative in as far as demonstrating any pathological change induced by the anesthetic. The glomerular vessels are distended with blood and the capillary loops usually fill the capsular space. The tubular epithelium, and especially that of the convoluted tubules,
is shrunken, the nucleus-plasma relationship has increased in favor of the nucleus, and the nuclei are hyperchromatic and stain intensely. The ascending limbs of Henle's loops either contain no stainable fat or a very small amount of fat in the form of dust-like particles.

A study of the response of the naturally nephropathic animals to Gréhant's anesthetic given in the same quantity per kilo as was the case with the control animals shows (with two exceptions, Experiments 4 and 6, Table II) that all the naturally nephropathic animals were rendered anuric by the anesthetic in ½ hour after the anesthetic was administered. At this period in the experiments the table shows that the anesthetic had induced a rapid depletion in the alkali reserve of all the naturally nephropathic animals which had become acutely anuric, while in the animals which at this period remained diuretic the alkali reserve had either undergone no change from the normal reading prior to the anesthetic or the reduction in the alkali reserve was not below 8.05. For example, the naturally nephropathic animal of Experiment 4 remained diuretic following the anesthetic and showed only a slight variation in the alkali reserve reading, 8.1 to 8.05. The animal of Experiment 6, which also remained diuretic, showed no change in the alkali reserve. The reading was 8 before and after the development of an anesthesia. The naturally nephropathic animals which became rapidly anuric show a depletion in the alkali reserve. The animal of Experiment 3 showed a reduction in the reserve alkali from 8.15 to 8, while in the animal of Experiment 8 the reserve alkali was reduced by the anesthetic from a normal reading of 8 to 7.9.

At this period of the experiments, the end of the first half hour, the functional response of the kidney was investigated by giving the animals caffeine, theobromine, or pituitrin. A study of Table II shows these substances, in the animals in which the anesthetic had induced a rapid depletion of the alkali reserve of the blood, to be of no diuretic value. The animals remained anuric. In the animal of Experiment 6, in which there had occurred no change in the alkali reserve from the normal reading, theobromine induced a free diuresis, the output of urine increasing from 2 to 10 drops per minute. In the animal of Experiment 4 in which the anesthetic had brought about a reduction in the alkali reserve from 8.1 to 8.05 caffeine was of no diuretic value.
At the end of the 1st hour of the anesthesia all the naturally nephropathic animals had become anuric. The alkali reserve of the blood had been reduced to 7.9 in all the animals except the dog of Experiment 10. The reserve alkali reading for this animal was 7.8. At this period of the experiment the functional response of the kidney was again tested by employing as diuretics theobromine, or solutions of urea and glucose. The kidneys of the naturally nephropathic animals were non-responsive to these substances which in the control animals had induced a marked diuretic effect. The anuria which has been associated with the development of an acid intoxication on the part of the anesthetized naturally nephropathic animals was unaffected by these diuretic solutions.

The experiments were continued for the third half hour period. During this time the animals remained anuric and the reserve alkali of the blood showed a progressive decrease in all the animals. At the termination of the experiments, 1½ hours after the first observations had been made, the reserve alkali readings for all the naturally nephropathic animals varied from a maximum reading of 7.85 to the extremely low reading of 7.45. The determinations of carbon dioxide tension in alveolar air at the close of the experiments varied between 22 and 10 mm. and showed the usual correlation with determinations of the alkali reserve of the blood.

In view of the previously mentioned observation that old animals were more susceptible to agents which induced an acid intoxication than were young animals, it is interesting to note that the two oldest naturally nephropathic animals gave evidence of having developed the severest acid intoxication. The animal of Experiment 10, 12 years old, had at the termination of the experiment an alkali reserve of 7.6 and a tension of alveolar air carbon dioxide of 18 mm., while the animal of Experiment 11, 13 years and 1 month old, had a reserve alkali of only 7.45 and a tension of alveolar air carbon dioxide of 10 mm.

The histological study of the kidneys of the naturally nephropathic animals after the establishment of an anuria by Gréhant's anesthetic has not shown any acute degenerative change or other evidence of vascular injury to the glomeruli. The capillary tufts usually fill the capsular space unless their distention has been prevented by a forma-
TABLE II.
Toxic Effect of an Anesthetic on the Functional Capacity of Normal and Naturally Nephropathic Kidneys.

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Anesthetic (Concentration)</th>
<th>pH 4 hr. after anesthetic</th>
<th>R. pH 4 hr. after anesthetic</th>
<th>Urine per min.</th>
<th>Diuretic</th>
<th>pH 1 hr. after anesthetic</th>
<th>R. pH 1 hr. after anesthetic</th>
<th>Diuretic</th>
<th>Urine per min.</th>
<th>pH 1 hr. after anesthetic</th>
<th>R. pH 1 hr. after anesthetic</th>
<th>Diuretic</th>
<th>Urine per min.</th>
<th>Carbon dioxide 1 hr. after anesthetic</th>
<th>Urine per min.</th>
<th>Fat in renal epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (control)</td>
<td>60 2 7.45 8.0 2</td>
<td>Theobromine 1%</td>
<td>5 7.45 8.0</td>
<td>Pituitrin 0.5 cc.</td>
<td>21 7.35 8.0</td>
<td>36 3 Tr.</td>
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<tr>
<td>2 (control)</td>
<td>60 1 7.4 8.1 2</td>
<td>Caffeine 1%</td>
<td>5 7.4 8.1</td>
<td>Glucose sol. 20%</td>
<td>26 7.4 8.1</td>
<td>39 6 &quot;</td>
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<tr>
<td>3</td>
<td>60 0 7.45 8.0 0</td>
<td>Pituitrin 0.5 cc.</td>
<td>0 7.4 7.9</td>
<td>Urea sol. 0.9%</td>
<td>0 7.1 7.8</td>
<td>19 0 L</td>
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<tr>
<td>4</td>
<td>60 2 7.4 8.05 0</td>
<td>Caffeine 1%</td>
<td>0 7.3 7.9</td>
<td>&quot; &quot; 0.9%</td>
<td>0 7.25 7.85</td>
<td>22 0 &quot;</td>
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<tr>
<td>5</td>
<td>60 0 7.45 7.8 0</td>
<td>Theobromine 1%</td>
<td>0 Not made.</td>
<td>Glucose sol. 20%</td>
<td>0 7.35 7.85</td>
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<td>6</td>
<td>60 2 7.35 8.0 2</td>
<td>Theobromine 1%</td>
<td>10 7.4 7.9</td>
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<td>21 0 &quot;</td>
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<tr>
<td>7</td>
<td>60 0 7.3 8.0 0</td>
<td>Caffeine 1%</td>
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<td>Theobromine 1%</td>
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<td>Theobromine 1%</td>
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<td>60 0 7.2 7.9 0</td>
<td>Caffeine 1%</td>
<td>0 7.4 7.9</td>
<td>Urea sol. 0.9%</td>
<td>0 7.35 7.8</td>
<td>21 0 &quot;</td>
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<tr>
<td>10</td>
<td>60 0 7.35 7.9 0</td>
<td>Theobromine 1%</td>
<td>0 7.4 7.8</td>
<td>Theobromine 1%</td>
<td>0 7.3 7.6</td>
<td>18 0 V. L.</td>
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<tr>
<td>11</td>
<td>60 0 7.4 8.0 0</td>
<td>Pituitrin 0.5 cc.</td>
<td>0 7.35 7.9</td>
<td>Urea sol. 0.9%</td>
<td>0 7.15 7.45</td>
<td>10 0 &quot;</td>
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*L* indicates large amount; *V. L.*, very large amount.
tion of connective tissue. The characteristic and constant change which is induced by the anesthetic is an acute swelling, vacuolation, and necrosis of the epithelium of the convoluted tubules, and a rapid accumulation of stainable fat in the ascending limbs of Henle's loops.

Fatty degeneration of a slight degree is occasionally seen in the degenerating convoluted tubule epithelium. The amount of stainable fat in the epithelium has shown a relation with the degree of acid intoxication in the various animals. The animals which have shown the greatest depletion in their alkali reserve and the lowest tension of carbon dioxide in alveolar air have also shown the greatest accumulation of fat in the degenerated epithelium, especially the epithelium of Henle's loops (Figs. 1 and 2).

DISCUSSION.

During the past 10 years numerous investigations have been concerned with the occurrence and significance of an acid intoxication in the acute and chronic nephropathies. As early as 1888 von Jaksch noted a decrease in the alkalinity of the blood in uremia and this observation was confirmed in 1898 by Brandenburg. Von Hosslin in 1909 noted in certain of the nephropathies a definite relation between the acidity of the urine and the amount of albumin and number of casts, and in a later paper after observing that very large amounts of alkali were necessary to reduce the acidity of the urine in nephritics, recommended rather indiscriminately the use of an alkali as a therapeutic measure. In 1912 Sellards, employing his alkaline tolerance test in a group of nephropathies, noted a retention of bicarbonate in the acute nephropathies with uremia, and at

about the same time Porges and Leimdörfer, using determinations of carbon dioxide tension as an index of an acid intoxication, concluded that there occurred in general a reduction of carbon dioxide tension parallel to the symptoms of uremia. The work of Straub and Schlayer which was confirmed by Barcroft and his pupils has apparently established the fact that in the type of acute kidney injury characterized by the symptom complex uremia, there is a direct connection between the uremic manifestations and an acid intoxication.

The question which is still undecided is concerned with the association of an acid intoxication in those acute and chronic nephropathies which have not developed symptoms of uremia and whether or not when such an intoxication occurs in these cases it should be considered as a retention acidosis due to the kidney injury or whether it should be looked upon as the cause of the renal injury. Both Sellards and Peabody in their studies of the chronic nephropathies reach the conclusion that the acid intoxication developing in these conditions is a retention acidosis and that the accumulation of non-volatile acids is not responsible for the kidney injury.

An analysis of the experiments which have been presented in the present study show that animals may have a severe type of chronic kidney injury that is largely localized in the glomeruli without developing an acid intoxication which can be detected by a depletion in the alkali reserve of the blood or by a reduction in the tension of alveolar air carbon dioxide. These animals show a slight retention of blood urea and a moderate reduction in the output of phenolsulfonephthalein. The minimum output of the dye in a 2 hour period for the naturally nephropathic animals has been 52 per cent. The kidneys of these animals show an epithelial element which is well preserved histologically and does not show any acute degenerative change. When these animals are anesthetized their response to the anesthetic as compared with normal animals shows the acid-base equilibrium of the naturally

nephropathic animals to be clearly unstable, for these animals rapidly develop an acid intoxication while the control animals maintain their normal acid-base equilibrium. Furthermore, when the acid-base equilibrium of these naturally nephropathic animals is only slightly altered in the direction of an accumulation of acid ions the animals become anuric and fail to respond to a variety of diuretic substances. In the control animals which are able to maintain their normal acid-base equilibrium during the period of anesthesia these diuretic substances induce a marked increase in the formation of urine. The development of the anuria by the nephropathic animals during the period of anesthesia which coincides with the occurrence of the acid intoxication has been constantly associated with an acute degeneration of the convoluted tubule epithelium and without the development of any acute injury to the vascular tissue of the kidney.

From these experiments it would appear that in the naturally acquired kidney injury of the dog in which the chronic pathology is largely confined to the glomeruli, the injury is not due to an acid intoxication. The experiments furthermore show that when such a kidney is subjected to an agent which leads to the formation and accumulation in the blood of acid bodies, the epithelium rapidly degenerates, and that with this degeneration the functional capacity of the kidney is arrested.

CONCLUSIONS.

1. The naturally acquired chronic glomerulonephropathies of the dog are not due to an acid intoxication.
2. Such an injury renders the acid-base equilibrium of the animal unstable and susceptible to an agent such as an anesthetic which tends to induce an acid intoxication.
3. When naturally nephropathic animals are anesthetized by Gréhant’s anesthetic, the principal anesthetic ingredient of which is chloroform, the animals develop an acid intoxication, and become anuric and non-responsive to diuretic substances.
4. The development of the anuria has been constantly associated with swelling, vacuolation, and necrosis of the convoluted tubule epithelium.
5. In the kidneys of these animals there occurs an accumulation of fat which is largely confined to the ascending limbs of Henle's loops and which shows a quantitative relation with the degree of acid intoxication.

EXPLANATION OF PLATES.

PLATE 49.

Fig. 1. Camera lucida drawing, Leitz oc. 2, obj. 6. The figure is from the kidney of the naturally nephropathic animal of Experiment 5, Table II. The glomerulus, a, has been to a large extent converted into a mass of connective tissue. The capillaries of the glomerulus have become oblitered and adherent to the thickened capsule. Surrounding the capsule is an area, b, of periglomerular fibrosis. At c is shown the acutely swollen and vacuolated convoluted tubule epithelium which is becoming necrotic. This animal after becoming anesthetized developed an acute acid intoxication, became anuric, and failed to show any diuretic effect from theobromine or a solution of glucose.

PLATE 50.

Fig. 2. Camera lucida drawing, Leitz oc. 2, obj. 6. The figure is from the kidney of the naturally nephropathic animal of Experiment 11, Table II. The glomeruli at a show both a capsular and an intracapillary formation of connective tissue. The smaller of the two glomeruli has undergone a partial hyaline degeneration. At b the thickening of the capsule is marked. At c is shown the acutely swollen convoluted tubule epithelium which is beginning to undergo necrosis. Very early during the anesthesia this animal developed an acute acid intoxication, became anuric, and failed to show any diuretic effect from either pituitrin or theobromine.
FIG. 1.

(MacNider: Nephropathic animals. I.)
FIG. 2.

(MacNider: Nephropathic animals. I.)