CONCERNING THE STABILITY OF THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN PREGNANT ANIMALS.*

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In previous publications1-4 studies have been undertaken which had as their object an investigation of the stability of the acid-base equilibrium of the blood in animals of different age periods. These studies were, furthermore, concerned with the ability of the physiological mechanism which maintains this equilibrium to stabilize it when it was subjected to the strain of certain intoxications and prevent this fundamental physicochemical balance of the organism from being interfered with. In one of these investigations it was shown that as the age of the organism increased, there was a decrease in the stability of the acid-base equilibrium of the blood. Such animals became more susceptible to the toxic effect of uranium nitrate and the general anesthetics.

The present study is concerned with the stability of the acid-base equilibrium of the blood in pregnant dogs at different periods of gestation and in different age groups, as contrasted with non-pregnant animals of the same age periods.

During the past 10 years 96 pregnant dogs have been studied in this laboratory in connection with various purposes. The observations recorded in this paper have gradually accumulated during this period. These animals varied in age from 11 months to 10 years and 4 months. The duration of pregnancy varied in the respective animals from 3 to

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10 weeks. The average duration of gestation in the dog is 9 weeks. Of these 96 animals, 22 have been eliminated from consideration in this study either on account of a lack of information concerning their age, or for the reason that the duration of gestation was not accurately known. The 74 pregnant animals included in this study may be divided into three groups on the basis of their age.

Group I is represented by twenty-two animals between the ages of 11 months and 3 years; Group II by thirty-four animals between 3 and 6 years of age; and Group III by eighteen animals between the ages of 6 years and 10 years and 4 months. The latter group is referred to in this paper as the senile group. In these groups are found animals that have varied in the duration of their pregnancy of from 3 to 10 weeks.

Observations on 68 normal, non-pregnant dogs serve as controls. These animals varied in age from 8 months to 11 years.

Technique.

Both the control and pregnant animals were kept in metabolism cages during each of the six periods of observation. The diet consisted of bread, butter, milk, and a small amount of cooked meat. No restriction was placed on the water intake by the animals. The dogs were catheterized once a day and the urine examined for albumin, glucose, and ketone bodies. The immediate functional capacity of the kidney was determined by the phenolsulfonephthalein test of Rowntree and Geraghty. Determinations of the alkali reserve of the blood (R. pH) were made by the method of Marriott, and these determinations were employed as an index of the acid-base equilibrium of the blood. The above mentioned observations on renal function were made in this study in order to eliminate any renal injury which might be responsible for a disturbance in the acid-base balance of the animals.

Control Observations.

Studies were made on 68 non-pregnant animals. The diet for these animals was the same as for the pregnant animals. Twenty-eight of these dogs forming Group I varied in age from 8 months to 3 years. Twenty-four animals in Group II were between 3 and 6 years of age, while sixteen animals forming Group III were between 6 and 11 years of age. All of the animals of Groups I and II had urines that were free from albumin, glucose, and ketone bodies. Casts were not present.

The elimination of phenolsulfonphthalein by the respective animals varied from 68 to 82 per cent. There was no evidence of a disturbance in renal function.

The reserve alkali of the blood was determined on 6 different days for each animal. The readings varied within the normal of from 8.0 to 8.15. In animals of such age groups, free from renal disease, the acid-base equilibrium of the blood shows a constant normal balance.

Sixteen of the control dogs, Group III, varied in age from 6 to 11 years. Two of these animals, Observation 32, 9 years and 2 months old, and the animal of Observation 60, 11 years old, showed evidence of renal disease. The urine contained a trace of albumin and casts. The elimination of phenolsulfonephthalein was 48 and 53 per cent by the respective animals. The reserve alkali of the blood for the animal of Observation 32 was 7.9, and for the animal of Observation 60, 7.95. With the evidence of impaired renal function shown by these animals, it is assumed that the disturbance in the acid-base equilibrium of the blood was due to a chronic nephropathy and should be looked upon as a retention phenomenon.

Two dogs of this old group of animals (Group III), Observations 18 and 41, had a normal urine. The elimination of phenolsulfonephthalein by the animal of Observation 18 was 74 per cent, and 69 per cent by the animal of Observation 41. These animals were studied over periods of 2 months. Fourteen reserve alkali determinations were made on each animal, and such observations uniformly showed a disturbance in the acid-base equilibrium of the blood.

The readings for the animal of Observation 18 varied from 7.85 to 7.95, while those for the animal of Observation 41 varied from 7.9 to 7.95. On two occasions the reserve alkali was 8.0. In these two senile animals with an absence of any functional evidence of renal disease there had developed a disturbance in some mechanism other than the kidneys which rendered the animals unable to maintain a normal balance in this physicochemical state of the blood.

The following conclusions are made for the control group of 68 non-pregnant dogs falling in the various age groups.

1. The young and adult females, Groups I and II, in the absence of renal disease constantly maintain a reserve alkali of the blood which is normal and which varies from 8.0 to 8.15.

2. The senile group of animals, Group III, with four exceptions, also maintained a normal alkali reserve of the blood. The reduction in the reserve alkali of the blood in two of these animals can be explained on the basis of a retention phenomenon secondary to renal disease. In the remaining two animals there was no evidence of renal disease. The lack of stability in the acid-base equilibrium of the blood in these animals was due to some other unknown factor.
Observations on Pregnant Animals.

74 pregnant dogs furnished the material for this study. The duration of gestation in the different animals varied from 3 to 10 weeks. These animals, as has been previously stated, were classified into three groups on the basis of their age. In all of the groups the observations recorded here were made either at the end of the first 4 weeks of gestation or within a week of the termination of gestation. A technique similar to that employed for the control groups of animals was used.

Group I.—Twenty-two dogs from 11 months to 3 years of age are included in this group. At the end of the 1st month of the gestation periods all of the animals had a normal urine, an elimination of phenolsulfonephthalein that varied from 68 to 82 per cent, and a reserve alkali of the blood that was normal and varied from 8.0 to 8.15. During the 8th week of the pregnancy of the animal of Observation 10, 3 years of age, and the 9th week of the pregnancy of the animal of Observation 8, 2 years and 9 months of age, the reserve alkali of the blood showed a reduction to 7.95. At this time the urine was normal and there was no reduction in the elimination of phenolsulfonephthalein. The remaining twenty dogs of this group showed no evidence of a disturbance in the acid-base equilibrium of the blood throughout the duration of the pregnancy.

Group II.—Thirty-four dogs are included in this group. The animals varied in age from 3 years and 1 month to 6 years. At the end of the 1st month of the gestation periods all of the animals had a normal urine and a normal elimination of phenolsulfonephthalein which varied from 68 to 76 per cent. All of the animals with one exception had a normal alkali reserve of the blood. The readings varied from 8.0 to 8.15. The animal of Observation 23, 6 years of age, at this stage of gestation had on 6 different days a reserve alkali of the blood of 7.9. The acid-base equilibrium of the blood was definitely disturbed. During the 8th week of the animal's pregnancy there developed an air-hunger type of breathing and associated with this a reduction in the reserve alkali of the blood to 7.8. At this time the animal was forming 442 cc. of urine in 24 hours. There was no albumin in the urine. The elimination of phenolsulfonephthalein was 68 per cent. On the following day the pregnancy came to a natural termination. On the 4th day following this the reserve alkali was 8.05.

During the 8th and 9th weeks of the pregnancies in the animals of Group II the following observations were made. Twenty-two of the animals came to the termination of the period of gestation with a normal urine, an elimination of phenolsulfonephthalein which was not below the minimum normal reading of 68 per cent, and reserve alkali determinations which were within the normal and varied from 8.0 to 8.1. Twelve of the animals gave evidence of a departure from the normal during these late weeks of the gestation period. Three of the twelve animals developed an albuminuria with casts. The amount of albumin in the
urine in these animals was 2.3 gm. for the animal of Observation 6; 2.0 gm. for the animal of Observation 5; and 0.4 gm. for the animal of Observation 13. The elimination of phenolsulfonephthalein was reduced in all of the animals from the normal output of 82, 69, and 70 per cent in the respective animals to 39, 41, and 28 per cent. The reserve alkali of the blood was reduced from the normal of 8.15 in the animal of Observation 6 to 7.9; in the animal of Observation 5, from 8.15 to 7.95; and in the animal of Observation 13, from 8.0 to 7.9. In these three dogs there was definite evidence of renal disease, which might explain the disturbance in the acid-base equilibrium of the blood.

The remaining nine animals in this group of twelve pregnant animals which gave evidence of a departure from the normal during the last 2 weeks of the gestation period had a normal urine and a normal elimination of phenolsulfonephthalein. All of these animals had developed a reduction in the reserve alkali of the blood which varied from 7.85 in the animal of Observation 22, 6 years of age, to 7.95 in the animal of Observation 11, 3 years and 2 months of age.

The animals of Group II, 3 to 6 years of age, have shown during the period of gestation two types of departures from the normal. Both types are associated with a disturbance in the acid-base equilibrium of the blood. The first type, represented by three animals in which such a disturbance occurred, can be explained as developing secondary to renal disease. The second type, which is characterized by a similar depletion in the reserve alkali of the blood, is not associated with any evidence of renal injury and is found to occur in the older members of the group.

Group III.—Eighteen dogs between 6 years and 10 years and 4 months of age are included in this group. During the 4th and 5th weeks of gestation fifteen of these animals had a normal urine and a normal elimination of phenolsulfonephthalein. The output of the dye in a 2 hour period varied from 69 to 81 per cent. Of this number eleven of the animals had a reserve alkali of the blood which was reduced below the normal and which varied from the maximum reduction to 7.9 in the animal of Observation 54 to the minimum reduction to 8.0 in the animal of Observation 20. The remaining four animals of the fifteen which had a normal urine and no reduction in the elimination of phenolsulfonephthalein failed to show any depletion in the reserve alkali of the blood. The reserve alkali determinations for these animals were respectively 8.05, 8.05, 8.1, and 8.15.

Three of the eighteen animals of Group III, Observations 3, 61, and 34, showed the presence of albumin, casts, and diacetic acid in the urine and had a decrease in the elimination of phenolsulfonephthalein to 38, 17, and 41 per cent in the different animals. In these animals with definite evidence of renal disease there was also a reduction in the reserve alkali of the blood. In the animal of Observation 3, the reserve alkali of the blood was reduced from 8.1 to 7.95; in the animal of Observation 61, from 8.15 to 7.9; and in the animal of Observation 34 from 8.15 to 8.0. One of these animals, Observation 3, during the 7th week of gestation developed convulsions and died. No observations had been made within 2 weeks
prior to the animal's death. At autopsy the kidneys showed marked epithelial
degeneration.

The animal of Observation 54 which had during the 5th week of gestation a
reduction in the reserve alkali of the blood to 7.9, with a normal urine and normal
elimination of phenolsulfonephthalein, gave birth prematurely to seven puppies
during this week. The animal was the oldest member of the group, 10 years and
4 months old.

The remaining sixteen animals of Group III representing the old animals of
the series, all of which have shown a reduction in the reserve alkali of the blood,
either with or without evidence of renal disease, completed their period of gestation.
In fourteen of these animals there was no further depletion in the reserve alkali of
the blood beyond the reading recorded during the 5th week of gestation. In two
of the animals, Observations 20 and 57, the reserve alkali underwent a secondary
reduction during these last weeks of gestation. In the animal of Observation 20
the reserve alkali was reduced from 8.0 to 7.9 and in the animal of Observation 57
from 7.95 to 7.85.

Excluding those pregnant animals with evidence of renal disease,
which may be assumed to have induced the recorded disturbance in
the acid-base equilibrium of the blood, the factor of the age of the
organism in influencing the stability of this equilibrium is shown as
follows by the animals when grouped according to age.

Group I was represented by twenty-two animals that varied in age
from 11 months to 3 years. At the end of the 1st month of gestation
all of these animals had a normal reserve alkali of the blood, a normal
urine with a normal elimination of phenolsulfonephthalein. At the
termination of the gestation period in this group of young animals,
only two members of the group showed any reduction in the reserve
alkali of the blood. These animals had a reserve alkali of the blood of
7.95. The urine was normal, and there was no reduction in the out-
put of the dye.

Group II was represented by thirty-four animals that varied in age
from 3 years and 1 month to 6 years. By the end of the 1st month of
gestation one of these animals had a reduced reserve alkali of the blood.
By the end of the 8th or 9th week of gestation in this group of older
animals nine showed a disturbance in the acid-base equilibrium of the
blood without any associated renal injury.

Group III was represented by eighteen senile animals, varying in
age from 6 years to 10 years and 4 months. During either the 4th
or 5th week of gestation in this oldest group eleven of the number had
a reduction in the reserve alkali of the blood which persisted throughout the latter weeks of gestation. None of these animals gave evidence of renal disease. By the end of the period of gestation, fourteen of the eighteen animals in this senile group, in which there was a normal elimination of phenolsulfonephthalein and a normal urine, showed a disturbance in the acid-base equilibrium of the blood.

This summary indicates that as pregnant animals advance in age the stability of the acid-base equilibrium of the blood decreases, and furthermore, that this instability is not due to coincident renal disease.

CONCLUSIONS.

1. The acid-base equilibrium of the blood as indicated by determinations of the reserve alkali of the blood remains constant in non-pregnant animals at different age periods. This statement does not imply that the acid-base balance of such animals at different age periods is a stable balance.

2. In pregnant animals of the same age periods as the control animals there may develop an instability of this equilibrium which is either associated with the occurrence of a renal injury and which may be looked upon as a retention phenomenon, or arises independently of such an injury. In this latter group of animals the disturbance in the equilibrium increases in frequency and is earlier in its appearance in the gestation period as the age of the organism increases.

3. In old and in senile pregnant animals some physiological mechanism other than that of the kidney becomes unable to stabilize the acid-base equilibrium of the blood with the result that as the pregnancy advances this physiological state of the organism (gestation) becomes pathological.