THE RELATION OF PHENOLS TO THE PRODUCTION OF UREMIA IN THE DOG

by

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V. M. D., University of Pennsylvania, 1948

A THESIS

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Surgery and Medicine

KANSAS STATE COLLEGE
OF AGRICULTURE AND APPLIED SCIENCE

1955

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INTRODUCTION

Many theories have been advanced to explain the toxic symptoms which characterize uremia. It was observed by early workers that phenols which are produced in the intestinal tract through bacterial action are absorbed and that their blood level is increased during renal insufficiency. Since phenol is known to be a protoplasmic poison, the elevation of this material was thought to produce the symptoms which were present in this syndrone. Recently using more specific chemical tests for determination of phenol levels it has been shown that such levels are not increased during uremia, but rather there is an increase in the aromatic hydroxy acid fraction. However, the elevated level of this material was found to be safely below the LD_{50}. These findings suggested that the essential cause of uremia is still unknown in humans.

That phenols might still be a factor in dogs with uremic poisoning was considered for several reasons. First, phenol poisoning has been reported in dogs which have eaten phenol containing products such as tar paper, linoleum, and other coal tar products. Secondly, it is known that bacterial decomposition of proteins yields certain phenolic compounds. Since dogs are by nature scavengers, it was thought that their intake of phenols would be higher than that of the human. Because of the irregularities which seem to exist concerning the importance of phenols in the canine, it was thought that experimental poisoning might aid in clarification of the problem. Also, since various

workers have shown that most phenols are detoxified in part by glucuronic acid, it was decided to ascertain its effectiveness as a therapeutic agent in phenol poisoning.

REVIEW OF LITERATURE

Since Richard Bright first observed the clinical picture of renal insufficiency in 1827 (Harrison and Mason, 18) many avenues have been explored in an attempt to find the etiological factor or factors of this syndrome. Prevost and Dumas (Harrison and Mason, 18) first discovered the association of renal insufficiency with elevation of the blood urea. From this discovery it was proposed that urea was the toxic substance producing the uremic syndrome. The work of Leiter (21) and Streicher (33) supported this, since they observed the production of symptoms of uremia in dogs as a result of intravenous administration of urea solution. Leiter (21) concluded that urea retention must play a part in the production of the uremic syndrome.

Contrary to this belief was the observation that very large amounts of urea were necessary to produce symptoms resembling uremia, and also there was no direct correlation between the severity of the symptoms and the urea level (18). It was noted by Peters and Van Slyke (27) that the symptoms observed in the urea experiments may have been due to dehydration, since no attempt was made to correct the water loss from diuresis. Bollman and Mann (6), working with dogs, transplanted the ureters into the intestines and found that these animals exhibited no

uremic symptoms despite a blood urea level of 800 milligrams percent. In so doing they eliminated the water loss by diuresis. This disproved that urea was, by itself, responsible for the uremic syndrome.

Landois (Harrison and Mason, 18), produced convulsions in dogs by application of creatinine to the brain and proposed that this substance was the etiological toxin of uremia. This hypothesis was questioned by Feltz and Ritter (Harrison and Mason, 18) who showed that intravenous administration of creatinine did not produce symptoms of uremia.

Another theory advanced was that of Ascoli (Harrison and Mason, 18). He suggested that there were two syndromes produced by renal insufficiency, one being urinary poisoning, due to the retention products and "renal uremia" characterized by convulsions and due to the action of "nephrolysins" from damaged renal tissue. Becher (4) pointed out that nephrolysins cannot be a factor since typical uremia is produced by bilateral nephrectomy.

Because uremia is manifested by various and sometimes opposing symptoms, such as stimulation and depression, later workers suspected more than one agent producing the uremia syndrome. Harrison and Mason (18) state, "In view of the number and diversity of the symptoms displayed by patients with uremia, it is rather surprising that most of the older authors looked for a single toxic substance". Workers then began looking for toxic agents which would produce one or more of the symptoms rather than the entire syndrome of uremia.

Becher and Hamann (Harrison and Mason, 18) noted an increase

of magnesium in uremia and believed it to be related to depression and the terminal fall in blood pressure. Later Hirshfelder noted that the levels which these men had observed were far below the level needed to produce depression of the nervous system in patients not treated with magnesium salts.

Harrison and Mason (18) state, "It is doubtful if magnesium retention in uremia, uncomplicated by magnesium therapy, is sufficient to account for any of the symptoms or signs of the syndrome".

Rabinowitch (28) noted an increase in the serum potassium level in severe renal insufficiency; however, it was shown that such levels were below the experimental levels needed to reproduce the neuromuscular irritability seen in uremia.

A decrease in the serum calcium level was observed by Marriott and Howland (22) in renal insufficiency. McLean and Leiter (24) observed that this decrease was in the ionized portion. It is believed that an increase in the inorganic phosphates is responsible for the decrease in calcium ions. Harrison and Mason (18) state, "In certain instances, however, the rise in inorganic phosphate in the serum is insufficient to cause a large alteration in calcium ion concentration and in certain cases certain organic anions, such as oxalates and citrate, may be augmenting the effects of inorganic phosphate". Most believe that oxalates and citrates play a secondary role in lowering the calcium ion concentration in uremia.

It has been shown by various workers (18) that introduction of phosphates, oxalates or citrates into the cisterna magna will

produce nervous symptoms which are sometimes seen in the uremic syndrome. That these neuromuscular effects are of central origin has been shown by Mason, et al. (23). They noticed that the symptoms produced paralleled a rise in the inorganic phosphate level and a fall in the calcium ion concentration of the cerebrospinal fluid. They also observed that anesthesia tended to relieve the neuromuscular irritability. It was noted that some dogs showed no irritability in spite of an increased cerebrospinal phosphate level and, conversely, some showed irritability where the phosphate level was not increased. They then concluded that there were opposing mechanisms at work -- one producing stimulation and the other depression.

Becher (4) in 1933 first suggested the importance of phenols. He noted the free phenols to be increased during the uremic state. The free phenols, which included phenol, paracreosol, indole and other related substances, are produced in the body from aromatic amino acids: tyrosine, phenylalanine and tryptophane. Banker and Schmidt (2) observed that the ingestion of a protein-free diet resulted in a marked decrease in urinary phenolic bodies in the dog. Becher (4) thought phenols to be derived mainly from putrefaction of protein in the intestine rather than the result of deamination, decarboxylation and oxidation of the aromatic amino acids. Harrison and Mason (18) have listed the chief evidence on which Becher bases his significance of the phenols as follows:

1. In chronic nephritis the increase in phenols in the blood tends to parallel the severity of the uremic manifestations

more closely than does that of the non-protein nitrogen.

2. In acute nephritis patients may have marked nitrogen retention without uremic symptoms and in such cases the blood levels are usually within normal limits.

3. Chronic phenol intoxication produced a symptom complex resembling in many respects that of uremia.

4. The introduction of aromatic amino acids into the rectum of persons with uremia increases the severity of the symptoms.

5. The onset of uremic coma coincides with the appearance in the cerebrospinal fluid of free phenols.

6. Phenol and phenol derivatives are themselves capable of producing and aggravating renal damage.

Becher further suggested that the accumulation of free phenols may be due to an interference of the conjugating mechanism.

Deichmann (9), in studying phenol, concluded that there are two general mechanisms for the disposal of phenol by the body other than excretion. It may be conjugated with sulfuric, glucuronic, and possibly other acids and it may undergo oxidation. It has been postulated that accumulation of non-toxic conjugated phenols in the body may interfere with the conjugation mechanism and therefore give rise to an increase of toxic free phenols. It has been observed by Williams (35) that the conjugation of phenol appeared to be influenced by a number of factors such as diet, fatigue, and temperature. It is reasonable to assume, then, that other factors could also influence this mechanism.

Becher's views were confirmed by Mason, et al. (23) who attributed the symptoms of depression and narcosis specifically to the presence of phenolic bodies in the cerebrospinal fluid.

In studying twenty-three uremic patients Dickes (15) found a direct correlation between the degree of cerebral depression and the blood levels of the phenols. He concluded that the total phenols had a greater correlation with the degree of cerebral depression than did the free or conjugated phenols. Roen (29) noted in an examination of thirty cases showing elevated blood urea values that, despite the fact that blood nitrogen retention was very marked, in no case without uremic symptoms was the blood phenol level above normal. He found, however, no direct correlation between the height of phenol levels and the severity of the symptoms. This raised some doubt concerning the importance of phenols in uremia.

Hartnett (19) determined the free phenol levels in fourteen cases of uremia using the method of Schmidt (30). He concluded that the free phenols had little if any effect in producing or intensifying the uremic syndrome. He also found that the free, conjugated, and total phenols did increase during uremia but concluded that it was not significantly enough to warrant their consideration as an important factor in this condition. He also noted that methods which are employed in previous determinations were non-specific and gave reason to doubt the validity of conclusions drawn concerning the relationship of free, conjugated, and total phenols to the uremic syndrome.

Schmidt, et al. (32) using methods which distinguished

between phenol and aromatic hydroxy acids found in studying twenty-nine patients with renal dysfunction and uremia that the free p-cresol-phenol fraction remained normal regardless of the severity of the uremic symptoms or the degree of nitrogenous retention. They observed, however, that the conjugated p-cresol-phenol fraction was found to be markedly elevated in the uremic patients. This level, however, was below the LD_{50} for this compound. They also found that the free and conjugated aromatic hydroxy acid fractions were greatly elevated in uremia, but that these sybstances were relatively non-toxic. They concluded that symptoms of uremia in man are apparently not due to free or conjugated phenolic compounds in the blood.

MATERIALS AND METHODS

Eight dogs between six months and one year of age were employed in the investigation. These animals were divided into four groups, each group containing one male and one female. Four of the dogs used were from the same litter and one of these was placed in each group. All animals were fed a commercial dog food (Kasco) which consisted of the following:

Protein	25%
Fibre	4%
Fat	8%
Ash	10%
N.F.E.	40%

Prior to being placed on experimentation a laparotomy was performed under sodium pentothal anesthesia and a liver biopsy was obtained for tissue section. This was done to decrease the

possibility of the presence of pathology of the liver prior to experimentation. One week following this operation phenol poisoning was initiated. Liquid phenol was mixed with water in approximately a 10 percent emulsion and was administered to each dog through a stomach tube. The dosage was based on body weight with each animal receiving a daily dose of .15 gram of phenol per kilogram of body weight. This dosage was increased weekly by a .05 gram per kilogram for a period of four weeks. Group I also received glucuronic acid orally. This material was in the form of sodium glucuronate monohydrate, which is the sodium salt of glucuronic acid. The dose of this material was two grams a day. Since glucuronic acid is structurally similar to glucose, being an incomplete oxidation product of glucose, its detoxifying activity was compared with that of dextrose. Therefore, Group II received four grams of dextrose orally together with phenol, while Group III received two grams of glucuronic acid intravenously and phenol. Injections were given via the cephalic vein. Group IV served as a control group receiving phenol alone. This procedure was continued for a period of four weeks. All dogs were weighed weekly and the dosage of phenol adjusted accordingly. Tissue sections were taken from the liver and kidney upon post mortem examination and microscopic studies were made of these tissues for pathological changes.

RESULTS AND DISCUSSION

The survival time of dogs may be seen in Table 1. The

greatest average time was 25 1/2 days, which was seen in Group III while the shortest period was 20 1/2 days. This was observed in Group I. Although it is noted that dog No. 3 died on the 17th day, and dog No. 6 survived the experimentation period of 28 days, there was no great variation in the group survival time. The average weight may be seen in Table 2. It is of interest to note that average group survival time is in relation to the average weight of each group. The heavier animals were apparently better able to withstand the effects of the phenols than were the smaller dogs. This observation is possibly explained when it is considered that the bodies of the heavier dogs in all probability contained more fat, thus having more reserve to withstand the stress which was placed upon them. Also, since the dogs were not fed individually, it is possible that the larger dogs received more food in relation to the smaller ones.

It was not observed that the other drugs administered had any deleterious or pronounced beneficial effect. In reviewing Table 1 it will be noted that Group III, which had the longest survival time, was treated with glucuronic acid intravenously. Dog No. 5 survived a period of 23 days, while dog No. 6 survived the entire course of treatment. It is seen, however, that dog No. 4, which received no glucuronic acid survived longer than did dog No. 5. It is probable then that the variation in the survival times could be ascribed to the weight of the animals and individual variation which is constant in the living organism. It does not seem likely that the toxicity of phenol is due to a deficiency of available glucuronic acid for conjugation.

Table 1. Survival time of dogs in days.

Group No.	Dog No.	7 days	14 days	21 days	28 days	Average Group Survival Time
1	1	.....				
	2	.....				20 1/2
2	3	.....				
	4	.....				22 1/2
3	5	.....				
	6	.....				25 1/2
4	7	.....				
	8	.....				21
Dosage Gms/Kg		0.15 day	0.20 day	0.25 day	0.30 day	

Toxic symptoms were not observed during the first week of treatment. Initially, the average dosage was 0.15 grams per kilogram of body weight. When the dosage was raised to 0.20 grams per kilogram, symptoms of poisoning were manifested. These symptoms became apparent within several minutes following administration of phenol by stomach tube. The first symptoms observed were dilation of the pupils. Generalized muscular twitching followed the above symptoms. When the dosage was increased, the twitching became pronounced until generalized convulsions resulted. These animals during convulsion seizures presented running-like movements with the front and rear legs while the head, neck and other parts of the body were held in rigidity. Heart rate, respiratory rate, and salivation was increased.

Table 2. Weight of dogs in kilograms during course of treatment.

Dog No.	Initial Weight	1st week	2nd week	3rd week	4th week	Average Initial Weight
1	5.9	5.9	5.45	-	-	4.75
2	3.6	3.9	4.1	3.6	-	
3	4.1	4.1	3.6	-	-	7.05
4	10.0	10.0	9.8	10.0	-	
5	4.1	4.1	4.3	4.1	-	7.05
6	10.0	9.5	10.0	9.5	9.5	
7	3.6	3.6	3.9	3.6	-	5.4
8	7.2	6.8	7.2	-	-	

Vomitition was not observed at any time during the course of the experiment. This was probably due to the local anesthetic action of phenol on the gastric mucosa despite the marked hemorrhagic gastritis that was present. The convulsions lasted from one-half hour to two and one-half hours, depending upon dosage of phenol given. Convulsions became more severe and prolonged after continuous daily administration of phenol. The intensity of these symptoms was probably due to tissue damage to the kidneys and liver, which inhibited efficient detoxification and excretion of phenol by the body. Administration of phenol consistently produced this reaction and at no time was a delayed reaction observed. Death resulted from respiratory failure and was preceeded by a deep coma.

Autopsy of each dog revealed a generalized toxemia.

Specifically there was a marked extensive intense gastritis and an enteritis which mainly involved the duodenal portion of the small intestine. The liver and kidneys were swollen, exhibiting a passive congestion. Microscopic sections of the liver showed changes similar to those described by Deichman et al. (11). There was a generalized cloudy swelling of the liver. Sections revealed areas of degeneration and necrosis in the centrolobular areas with the liver cord cells appearing enlarged, pale and granular. Some nuclei were swollen while others showed pyknosis and karyorrhexis. The areas of degeneration showed little inflamatory response other than a slight degree of lymphocytic infiltration in certain focal areas. The normal degree of variation was noted in these animals.

Sections of the kidneys revealed generalized edema and cloudy swelling, especially in the tubular portion. The degenerative changes ranged from cloudy swelling to fatty degeneration and necrosis. The epithelial cells lining many of the tubules were swollen, and as a result the lumina of these tubules were small and even occluded. Other tubules contained cellular debris and casts. Tubular cells of these tubules revealed the nuclei undergoing degenerative changes such as karyolysis, pyknosis, and karyorrhexis. The lumen of these contained a granular network composed of cytoplasm from the ruptured or broken cells. The glomeruli exhibited little or no pathological changes. The glomeruli showed some cellular infiltration and degenerative changes. There was slight proliferation of the stroma of the glomeruli and interstitial tissue.

In considering the amount of material, the period of time and the changes which are necessary to produce death of the animal, it is apparent that the body has a very efficient detoxification mechanism for phenol. It has been shown that this mechanism can counteract a large dose of phenol in a relative short time. It was apparent that it is very unlikely for free phenols to occur in excess in the body. As mentioned earlier in this paper, Becher (4) believes that phenols are produced from intestinal putrifaction of aromatic amino acids. Phenols arising from this action are few in comparison to the amount necessary to produce poisoning. It has been shown that these phenols are readily detoxified by the conjugation mechanism Deichman (9).

From these observations and studies it seems unlikely that phenols are important in the production of uremia in the dog. Another observation in support of this is that central nervous symptoms as produced by ingestion of phenol are not commonly observed in canine uremia. The uremic syndrome observed in the canine is characterized by depression. These observations would suggest, as did Schmidt concerning uremia in humans, that the essential cause of the uremic syndrome in the canine is unknown.

SUMMARY AND CONCLUSIONS

1. Eight dogs were poisoned with oral doses of phenol. These dogs were divided into four groups. Besides phenol, one group received glucuronic acid orally, one group glucuronic acid

intravenously and one group dextrose orally. The remaining group served as a control. Symptoms and survival times were noted and upon autopsy microscopic tissue studies were made of these animals.

2. Phenol poisoning probably never occurs naturally in dogs, since they are capable of handling relative large amounts without observable symptoms of distress.

3. Phenol is a protoplasmic poison and at high levels will produce damage to liver and kidneys.

4. The toxicity of phenol is evidently not due to a deficiency of glucuronic acid for the conjugation mechanism, and furthermore, the administration of glucuronic acid by oral or intravenous route is of no observable value.

5. It is very unlikely that phenols play any important part in the production of the uremic syndrome in dogs.

6. The pathogenesis of the uremic syndrome is essentially unknown in the canine.

ACKNOWLEDGMENT

The writer wishes to express his appreciation to Dr. M. J. Twichaus and thank him for the aid and advice so kindly given in the course of this work and in the preparation of this thesis.

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ABSTRACT

It was observed by early workers that phenols which are produced in the intestinal tract through bacterial action are absorbed and that their blood level is increased during renal insufficiency. Since phenol is a protoplasmic poison, its elevation was thought to justify the symptoms which were present. Recent workers using more specific chemical tests found that phenols were not increased during uremia. It was concluded that the essential cause of uremia in humans is unknown. Phenols were still considered as being a factor in uremia of dogs for several reasons. First, since phenols are produced from intestinal putrefaction of aromatic amino acids and since dogs are by nature scavengers, it was thought that their intake of phenols would be higher than that of humans. Also, poisoning has been reported in dogs from ingestion of coal tar products. It was thought that experimental poisoning might aid in clarification of the problem. Also, since phenol is detoxified in part by glucuronic acid, it was decided to determine its effectiveness as a therapeutic agent.

Eight dogs between six months and one year of age were employed in the investigation. These animals were divided into four groups, each group containing one male and one female. Four of the dogs used were from the same litter and one of these was placed in each group. Prior to being placed on experimentation, a laparotomy was performed and a liver biopsy obtained for tissue section. This was done to eliminate the possibility of

the presence of pathology of the liver prior to experimentation. One week following this procedure, the administration of phenol was initiated. Liquid phenol was mixed with water in approximately a 10% emulsion and given through a stomach tube. The initial dosage was 0.15 grams per kilogram of body weight and this dosage was increased weekly by 0.05 gm/kg. Group I also received two grams of glucuronic acid orally in the form of sodium glucuronate monohydrate which is the sodium salt of glucuronic acid. Group II received four grams of dextrose orally together with phenol while Group III received two grams of glucuronic acid intravenously and phenol. Group IV served as a control receiving phenol alone. This procedure was continued for a period of four weeks. All dogs were weighed weekly and the dose of phenol adjusted accordingly. Upon post mortem examination, sections were taken from the liver and kidney and microscopic studies were made.

Results of the experiment revealed no marked variation in the survival time. It was noted that the heavier dogs were better able to withstand the effects of phenol poisoning than were the smaller dogs. The administration of dextrose or glucuronic acid produced no pronounced beneficial effect. It was concluded in these experiments that the toxicity of phenol is not due to a deficiency of available glucuronic acid for conjugation.

Symptoms of poisoning did not occur until the dosage level reached 0.2 gm/kg. Symptoms observed varied from slight muscular twitching to generalized convulsions. Recovery from convulsions

was usually complete within two and one-half hours or less, depending upon the amount of phenol given. It was noted that the symptoms produced are not commonly observed in canine uremia. Death of the animals was due to central respiratory failure and was preceded by deep coma.

Post mortem examination revealed a generalized toxemia. Microscopic examination of the liver revealed areas of degeneration and necrosis. There was little inflamatory response other than a slight degree of lymphocytic infiltration in certain areas. Examination of the kidneys revealed degenerative changes ranging from cloudy swelling to fatty degeneration and necrosis. These changes were mainly confined to the tubules with little change being noted in the glomeruli.

The observations and studies made suggest that the dog can tolerate relative large doses of phenol over a relative long period of time. It is considered unlikely that a sufficient amount of phenol can be produced in the body to produce symptoms of uremic poisoning. It has been shown that the body has a very efficient mechanism for the detoxification of phenol. It is therefore suggested that phenols do not play an important part in the production of the uremic syndrome in the dog.