

## Studies on the Alimentary Tract of the Merino Sheep in South Africa. XXI.—The Toxicity of Urea to Sheep under Different Conditions.

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### INTRODUCTION.

DURING the course of studies on various factors affecting the activity of the ruminal flora it was decided also to include the effects of urea. Preliminary experiments disclosed the fact that even moderate doses of urea, as little as 10 gm., were frequently highly toxic to sheep that had been kept on a diet of poor quality grass hay previous to dosing. Sheep adapted to a ration of lucerne hay, on the other hand, were found to be more tolerant. Similarly Hoflund, Quin and Clark (1948) reported the sudden death of sheep adapted to a poor diet following the administration of 200 gm. of casein.

The feeding of urea to ruminants as a partial source of protein has been the subject of numerous publications in recent years. McNaught and Smith (1947) published a review on the subject. With regard to the toxicity of urea these authors state "While discussing feeding trials it will be well to mention that N.P.N. in excess may be toxic. Since in the rumen urea is converted with great rapidity to ammonia, large amounts of urea, particularly if given all at one time, might be expected to have harmful and even fatal results." No references to direct reports of such toxicity are cited.

### SYMPTOMS OF ACUTE POISONING SHOWN BY SHEEP AFTER BEING DOSED UREA.

In acute cases clinical symptoms appeared from 30 to 60 minutes after dosing. Dullness was followed by marked hyper-aesthesia and severe muscular twitches over the whole body. Moderate to severe bloating frequently occurred at this stage. Severe tetanic spasms of the skeletal musculature of the whole body then set in. The animals went down with the legs stiffly extended and the claws abducted. Stimulation by touch or sound caused marked exacerbation of the spasms, in fact the whole syndrome was typical of strychnine poisoning. Later the breathing became extremely laboured and the regurgitation of ruminal contents frequently occurred just before death.

### *Post Mortem Findings.*

On *post mortem* examination the cause of death was found to be acute circulatory collapse with severe generalised venous stasis. In some animals this was more marked in the pulmonary circulation as shown by hydrothorax and severe

pulmonary congestion and oedema. Haemorrhages under the epi- and endocardium were almost invariably present. In other cases the congestion was more severe in the splanchnic area, affecting the liver and spleen and causing haemorrhagic diathesis in the small intestines. In all cases there was severe degeneration of the liver and kidneys. On microscopic examination these organs showed severe fatty degeneration scattered over the whole lobule of the liver and affecting the tubules of the renal cortex. It is of interest to note that these lesions were present even in animals which died within one hour after being dosed.

The ruminal contents of all the animals smelt strongly of ammonia.

#### THE EFFECT OF UREA ON RUMINAL MOTILITY.

By using sheep with permanent ruminal fistulae and giving smaller non-lethal doses, it was found that the introduction of urea into the rumen was followed by a decrease or entire cessation of ruminal motility. This was associated with an ammoniacal smell from the ingesta and a sharp rise in the pH.

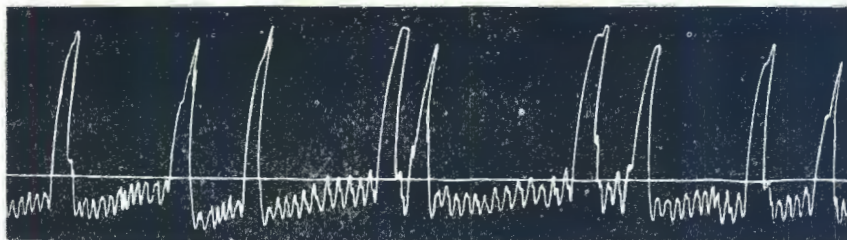
Here again it was found that sheep on a diet of poor quality grass hay were more susceptible than those on lucerne hay. Although a wide variation in susceptibility was found in both classes of animals, from observations on some 20 sheep it can be stated that a dose of 10 to 15 gm. was usually sufficient to cause ruminal paresis in sheep on grass hay, whereas 20 gm. was required for animals on lucerne.

Recovery of ruminal motility usually took place in 3 to 4 hours although in individual cases the paralysis persisted for 48 hours.

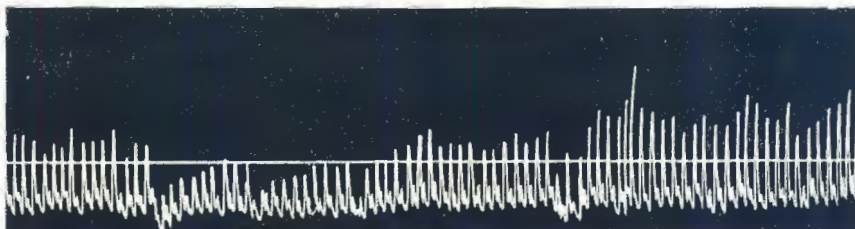
The effect on ruminal motility of dosing 10 gm. of urea into the rumen of a grass hay fed sheep is illustrated in Figure 1.

FIGURE 1.

*The Effect of Dosing 10 gm. of Urea into the Rumen of a Grass Hay Fed Sheep.*



Normal (before dosing) pH 7.15.



Ruminal stasis and dyspnoea 30 minutes after dosing 10 gm. urea. pH 8.15.  
(Each tracing 5 minutes duration.)

The dosing of urea almost invariably caused a decrease in food consumption over the following few days. This might have been associated with ruminal stasis or with a general derangement of the ruminal flora which could be demonstrated by decreased sugar fermentation and retarded cellulose digestion when tested *in vitro*.

#### THE CAUSES OF TOXIC EFFECTS AFTER DOSING UREA.

##### (a) *Ruminal Paralysis.*

The cause of the ruminal paralysis subsequent to dosing urea was later proved to be associated with the increased alkalinity of the ruminal contents following the formation of ammonia.

##### (b) *Tetanic Spasms.*

The actual toxic agent responsible for the acute tetanic spasms and circulatory collapse already described, has not been identified. It is well-known that urea itself is almost non-toxic but in order to eliminate this obvious possibility a sheep was injected with 20 gm. of urea intravenously without any ill-effects.

It was thought most likely that the symptoms were due to the absorption of ammonia, acting either on the acid base ratio of the blood or as a specific nerve poison. This would, however, appear not to be the case as several sheep injected intravenously with relatively large amounts of ammonia failed to exhibit the typical symptoms expected.

In one instance a sheep weighing 58 lb. was injected intravenously with 7 c.cm. of *ammon. fort.* diluted to 700 c.cm. with saline. This was divided into three equal doses given over the course of two hours. At each injection the animal showed dyspnoea. After the third treatment it passed into a deep coma with complete relaxation of the skeletal muscles. Complete recovery took place in approximately one hour. This treatment was repeated on three consecutive days with identical results. The animal was slaughtered on the fourth day and on *post mortem* examination the organs were found to be entirely normal.

There is also evidence to show that the acute symptoms are not directly caused by an alkalosis. In subsequent experiments it was found that raising the pH of the ruminal contents by other alkalies caused ruminal paralysis but muscular spasms and circulatory collapse were not encountered.

#### THE INFLUENCE OF THE REACTION OF THE RUMINAL CONTENTS ON THE TOXICITY OF UREA.

In view of the fact that sheep suffering from acute urea poisoning showed the presence of ammonia and a high pH in the rumen, the administration of acid was tried as an antidote. Dilute acetic acid given either into the rumen or intravenously was found to be extremely beneficial even when the symptoms were advanced.

This indicated that the presence of free acid in the rumen at the time of dosing would protect against urea poisoning. Accordingly six sheep which had previously been fed on a ration of grass hay were each dosed with 24 gm. of urea per 100 lb. body weight. Two of the animals also received 40 c.cm. of acetic acid, suitably diluted, while another two were given 40 gm. of sodium bicarbonate.

The results were as follows:—

1. *Urea alone.*—One died after 3 hours while the other showed no symptoms.
2. *Urea plus sodium bicarbonate.*—Both died within one hour.
3. *Urea plus acetic acid.*—Neither showed any symptoms.

The toxicity of urea was thus shown to be increased by alkali and decreased by acid.

As it is well-known that an active ruminal flora readily ferments sugar to organic acids, this indicated that sugar in the rumen would also protect against urea poisoning provided it could be rapidly fermented.

#### THE EFFECTS OF DIET ON THE TOXICITY OF UREA.

As already stated, sheep on a ration of poor quality grass hay were found to be more susceptible to urea poisoning than those on lucerne hay. This indicated that the toxicity of urea was linked with the constitution and activity of the ruminal flora which factors would in turn depend on the diet and the state of digestion. It was, therefore, decided to conduct an experiment on the following lines. Twenty four sheep were divided into two main groups, the one group being placed on a ration of lucerne hay and the other on grass hay. This preliminary treatment was continued for two weeks in order to allow the ruminal flora to become fully adapted. Each of these two main groups was then subdivided as follows:—

12 Sheep.....	{ (6) Starved for 72 hours before dosing.	{ (3) Dosed urea alone. (3) Dosed urea and 20 gm. sucrose.
	{ (6) Not starved before dosing	{ (3) Dosed urea alone. (3) Dosed urea and 20 gm. sucrose.

In order to ensure that both the urea and sucrose entered the rumen, these substances were injected directly into the organ by means of a long hypodermic needle inserted through the flank. This method of administration proved entirely satisfactory and in itself had no ill effects on the animals.

#### RESULTS.

##### A. Sheep on Grass Hay Ration.

The sheep on the grass hay ration were dosed with urea at the rate of 18 gm. per 100 lb. body weight. The results are shown in table 1.

TABLE 1.

*The Effect of Dosing Urea into the Rumen of Sheep fed on Grass Hay.*

Treatment.	Sheep No.	Result.
Not Starved.....	1	No effect.
No Sugar.....	2	Appetite reduced.
	3	Appetite reduced.
Not Starved.....	1	Appetite slightly reduced.
Sugar dosed.....	2	No effect.
	3	No effect.
Starved.....	1	Died.
No Sugar.....	2	Appetite reduced.
	3	Died.
Starved.....	1	Died.
Sugar Dosed.....	2	Died.
	3	No effect.

It will be noted from the above table that fatal cases of acute poisoning only took place among the sheep that had been starved for 48 hours prior to dosing urea. Under these circumstances the sugar had no protective action. This may be ascribed to the fact that the starvation so reduced the activity of the flora to ferment the sugar (Quin 1943) that insufficient organic acid was formed.

The administration of similar amounts of urea to sheep in full digestion merely caused subsequent inappetence. In this case the simultaneous administration of sucrose had a beneficial effect.

#### B. Sheep on a Ration of Lucerne Hay.

The animals in this group were dosed urea at the rate of 24 gm. per 100 lb. body weight, as compared to 18 gm. given to the grass hay fed sheep. Despite this higher dosage none of the animals showed signs of acute poisoning. The animals that were fed up to the time of dosing showed a slight decrease in appetite the following day. This reaction was more marked and more prolonged in the sheep that were starved prior to dosing but this effect could have been expected after starvation alone. (Quin, Oyaert and Clark, 1951).

The experiment was later repeated using 36 gm. of urea per 100 lb. body weight with exactly similar results.

#### THE EFFECTS OF INCREASED PROTEIN INTAKE ON THE TOLERANCE FOR UREA.

In view of the above findings it was decided to investigate the effect of an increased protein intake on the tolerance for urea. Four sheep were placed on a ration of poor quality grass hay but in addition two of them received 150 gm. of casein per day. A week later they were dosed with urea as indicated in Table 2.

TABLE 2.

Diet.	Sheep No.	Dose Urea (gm. per 100 lb. body weight).	Result.
Hay only.....	1	18	Died. In extremis*
	2	18	
Hay plus 15 gm. Casein.....	3	18	No effect. No effect.
	4	36	

\*Saved by dosing acetic acid.

As will be seen the addition of protein to the diet resulted in greater tolerance for urea, probably by conditioning the ruminal flora to a high plane of nitrogen metabolism.

#### DISCUSSION.

As far as the authors are aware no previous reports of what might be termed acute urea poisoning in ruminants have been published. It is admitted that the present investigation was made on the effects of relatively large amounts of urea

administered in single doses and the result would not apply had even similar amounts been fed over the course of the day. Nevertheless, the results may have considerable significance in the elucidation of the aetiology of gastric disturbances associated with urea feeding. What may be of even greater importance is the observation that symptoms identical to those of urea poisoning may be brought about by a sudden rise in protein intake.

Urea is rapidly broken down in the rumen to ammonia, which, if it accumulates, causes a rise in the pH. of the ruminal contents and consequent ruminal paresis. In the presence of sufficient readily available carbohydrate, however, an active flora will rapidly utilise the ammonia as a source of nitrogen and so prevent its accumulation. The toxicity of urea therefore depends on the activity of the ruminal flora and the presence of sufficient available carbohydrate.

These results are in complete uniformity with those of Sapiro, Hoflund, Clark and Quin (1948) who showed that the rate of disappearance of both nitrate and nitrite from ruminal ingesta depended on the basic diet and the presence of sugars. Furthermore sheep on a poor diet were found to be highly susceptible to nitrite poisoning, as shown by methaemoglobinaemia, when dosed with nitrate. The simultaneous administration of sugar protected against such poisoning.

It would, therefore, appear that the normal nitrogen metabolism within the rumen depends on the presence of an active flora and sufficient readily available carbohydrate. In the absence of either of these factors toxic nitrogenous products may be formed.

The cause of the sudden death associated with muscular spasms and circulatory collapse could not be established. From the evidence available it would appear not to be due to the absorption of urea or ammonia, nor to a direct disturbance of the acid-base ratio of the blood. It might be postulated that under certain conditions including an alkaline medium, the flora utilizes the ammonia for the production of toxic intermediary products.

#### SUMMARY.

The dosing of urea into the rumen of sheep caused acute intoxication characterised by atony of the rumen, muscular spasms and sudden death due to circulatory failure.

The toxicity of urea was found to depend on the activity of the ruminal flora, as determined by the basic diet, and the presence of available carbohydrate.

Toxic symptoms after dosing urea were associated with the formation of ammonia and a high pH. of the ruminal contents. They could be prevented or alleviated by the administration of acid.

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