Onderstepoort Journal of Veterinary Science and Animal Industry,
Volume 17, *Numbers* 1 *and* 2, *July and October*, 1941.

Printed in the Union of South Africa by the
Government Printer, Pretoria.

Poisoning by Voided Urine.

By S. J. VAN DER WALT and DOUW G. STEYN, Section of Pharmacology and Toxicology, Onderstepoort.

Instruction.

In the course of the last few years several cases of suspected poisoning by human urine in cattle have been brought to our notice. The animals drank urine contained in night-soil buckets.

There are two forms of urine poisoning: (1) where the urine is taken *per os*, and (2) where urinary excretion is defective, either due to diseased kidneys (nephritis) or to a blockage of the urinary tract e.g. by calculi.

The latter form of poisoning is of importance owing to the frequent occurrence of calculi in the urinary tracts of animals (" pis-goed ") in certain parts of the Union of South Africa (Steyn and Reinach, 1939).

This paper, however, concerns itself only with the first form of poisoning.

The main constituents of mammalian urine are water, inorganic salts, urea and small quantities of other organic substances.

The concentration of the inorganic salts in urine is so low that tremendous quantities of urine would have to be consumed to cause acute poisoning by these salts. They are therefore of no great importance as far as poisoning by urine is concerned. The same applies to the organic constituents other than urea, such as creatine and creatinine.

Fröhner (1919) describes a case in which a year old sheep died within six hours after consuming 0·5 litres of fresh human urine. The symptoms consisted of a general cerebral and spinal paralysis. Such cases, resembling ptomaine poisoning, he ascribes to normal constituents of urine such as novain, vitiatin, gynesin, etc.

Haase (Fröhner, 1919) observed tympanites and general paralysis in four sheep which had consumed fresh human urine.

In horses which had drunk fountain water contaminated with liquid manure, Göckel, quoted by Fröhner (1919), observed listlessness, somnolence, swaying and a slight swelling of the lymphatic glands.

Fröhner further rightly remarks that the cause of poisoning in these cases could not be urea since urea causes tetanic spasms and not paralysis.

Riggio (Fröhner, 1919) produced such tetanic spasms in experimental animals with equine urine.

The following information is taken from Lewin (1929). Normal human urine in large quantities is toxic causing myosis and symptoms of curare poisoning, 40-60 c.c. of urine of adult human beings and 60-120 c.c. of that of infants being fatal for a 1·0 Kg. animal. Urine from which the ammonia has been removed is still toxic. Furthermore since relatively large quantities of urea are non-toxic and since it is said to cause tetanic spasms in rabbits and dogs when injected intravenously in large quantities, the part played by this substance, as far as the toxicity of urine is concerned, is doubtful. The chief toxic action of urine is due to bases (xanthin group and others). These substances occur in normal urine and are present in increased quantities in diseased persons. Urine passed during the day is more toxic than, and has a different action from, that passed during the night. Dogs are 2½ times as resistant to urinary poisons as rabbits. In the urine of diseased persons there may be an increased quantity of toxic substances and the nature of these substances may vary. The urine is more toxic in cases of infectious diseases, a portion of the toxic substances being probably formed in the alimentary tract and excreted in the urine after absorption. Different toxic substances occur in the urine in different diseases e.g. pleurizin in pleuritis and glycozyamidin in measles. The same is observed in chronic diseases, e.g. cancerin cases of carcinoma and leukomaïn in epileptics after an attack. The urine of persons suffering from pathological conditions of the liver causes gastro-enteritis, decrease of the body temperature, exophthalmus, mydriasis and somnolence following on convulsions.

Pfeiffer and Albrecht (Lewin, 1929) examined the urine of diseased persons by subcutaneous inoculation of the urine into guinea pigs and found that—

(1) the toxicity of the urine under physiological and pathological conditions is, according to the temperature reaction, to a great extent independent of the specific gravity and thus of the salt content as well as the albumen and free acid content of the urine;

(2) the toxicity of those urines with an increased toxicity is simply an increase, measurable by the temperature reaction, of the normal toxicity of the urine;

(3) the urine of guinea pigs possesses two toxic principles: (*a*) the ordinary toxic principle and (*b*) a toxic principle with a necrotic action on the subcutis of rabbits. The second principle, which has never been encountered in human urine, is independent of the quantity of the first.

With the above method, viz., subcutaneous inoculation, Pfeiffer and Albrecht found an increased toxicity of the urine in cases of epilepsy, chorea, infectious diseases (pneumonia, pulmonary tuberculosis) and others and a decreased toxicity of the urine in cases of chronic nephritis.

Onderstepoort Experiments.

The symptoms of general paralysis, in the absence of tetanic spasms, as described by Fröhner (1919), Lewin (1929) and thers have not been encountered in our experiments on rabbits and sheep with fresh and decomposed human urine.

Quantities of up to 3·0 litres of fresh human urine, collected overnight and administered * to a sheep the following morning, caused no ill effects whatsoever. The urine in these cases was clear with a normal odour and a neutral

* All the experimental animals were drenched by means of a stomach tube.

reaction to litmus. Furthermore human urine which had been standing for 36 hours was administered to a sheep without causing any ill effects. Of this urine, which was slightly alkaline and had an offensive odour and showed a heavy whitish precipitate, this animal received 2·5 litres in two doses at an interval of seven hours.

The main symptoms observed in our experiments were tetanic convulsions and these were only observed after the administration of decomposed urine which had become strongly alkaline with a heavy whitish precipitate; such urine had an offensive odour markedly tainted with that of ammonia.

The following serves to illustrate:—

Sheep 57164 (6 tooth; 32·5 Kg.) was drenched, after having been starved for 24 hours, at 11 a.m. on 2.12.40 with 3·0 litres of human urine which had been collected from adults and children during the nights of 29.11.40-30.11.40, 30.11.40-1.12.40 and 1.12.40-2.12.40. The urine which showed a heavy white precipitate was alkaline and emitted a strong smell of ammonia.

Almost immediately after drenching the sheep started to shiver, this being at first most noticeable in the muscles of the abdomen. From 5 minutes after drenching paresis was evident, the sheep staggering about and placing its limbs in abnormal positions in order to retain its equilibrium. Ten minutes after drenching the paresis had progressed to general paralysis, the animal collapsing and lying quietly on its side. At this stage the respiration was accelerated and superficial whilst the pulse was accelerated and weak. Ruminal movements were in abeyance. The animal remained in this state for 5 minutes when tetanic spasms of the whole body (indistinguishable from those seen in tetanus and strychnine poisoning) set in. The spasms were repeated at short intervals. The respiration and pulse became laboured. Vomition was observed. The animal died in a tetanic spasm 25 minutes after drenching. After death relaxation of the cardia and oesophagus occurred so that a large quantity of ruminal contents flowed from the nose and mouth.

Post mortem appearances.—General cyanosis; slight hydropericardium; pronounced emphysema and slight hyperaemia of the lungs with froth in the air passages; fair degree of hyperaemia of the mucosa of the bronchi, trachea, larynx and pharynx; regressive changes in the myocardium; hyperaemia of, and severe regressive changes in, the liver; hyperaemia of, and regressive changes in, the kidneys; hyperaemia of the mucosa of the rumen, omasum, abomasum and small intestine; slight hyperaemia of the mucosa of the caecum.

Sheep 56486 (full-mouth; 45·5 Kg.) was also drenched with 3·0 litres of the above urine but the sheep had not been starved.

With the exception of tympanites the symptoms in this case were very similar to those observed in sheep 57164. The sheep died 25 minutes after drenching, ruminal contents again flowing from the nose and mouth.

Post mortem appearances.—General cyanosis; tympanites of the rumen; slight hydropericardium; ascites; hydrothorax; fair emphysema and slight hyperaemia of, and occasional haemorrhages in, the lungs; slight hyperaemia of the mucosa of the bronchi and trachea which contained froth; regressive changes in the myocardium; hyperaemia of, and regressive changes in, the liver and kidneys; fair degree of hyperaemia of the mucosa of the abomasum and small intestine; slight hyperaemia of the mucosa of the caecum.

Rabbit A (1·6 Kg.) was drenched with 120 c.c. of human urine which had been standing for 36 hours. The urine was alkaline and showed a heavy white deposit; the odour was offensive and markedly tainted with that of ammonia.

Almost immediately after drenching, the animal became listless and paretic; the paresis rapidly progressing to general paralysis. At this stage the animal was lying on its sternum with the forelimbs extended and the head resting on the floor of the cage. From approximately ten minutes after dosing slight spasms, occurring at short intervals, set in. These spasms at first caused the whole body of the rabbit to give a rapid jerk. The duration and intensity of the spasms rapidly increased to tetanic spasms indistinguishable from those seen in strychnine poisoning and tetanus. For a few minutes the tetanic spasms rapidly succeeded each other but from then on occurred only after long intervals. In these intervals the animal was lying on its side with accelerated pulse and respiration whilst repeated slight spasms caused the body to jerk. The animal died in a tetanic spasm 25 minutes after having been drenched.

Post-mortem appearances.—General cyanosis; severe emphysema of, and numerous petechiae in, the lungs; hyperaemia of, and regressive changes in, the liver; hyperaemia of the kidneys; slight hyperaemia of the mucosa of the stomach.

Since urine, when fresh, causes no ill effects when administered *per os* in fairly large quantities, but becomes highly toxic when allowed to stand for some time, it is obvious that urea itself cannot be the toxic agent but that some toxic substance is formed during the process of decomposition of the urine.

When urine is allowed to decompose the urea is broken down by bacterial action to ammonia. That ammonia is the toxic agent, which forms in urine when allowed to stand, is clearly shown by the great similarity of the symptoms seen in poisoning by ammonia to those seen in poisoning by decomposed urine. The following experiments, in which the lethal dose of ammonia was determined, serve as an illustration.

The rabbits were drenched with Merck's Liquor Ammonii Caustici (±32·5 per cent. NH_3).

Rabbit A. (1·5 Kg.) was drenched with 0·75 c.c. of Liquor Ammonii Caustici in 80 c.c. of tap water. The rabbit became slightly listless and went off its feed for a day.

Rabbit B. (1·75 Kg.) was drenched with 1·5 c.c. of Liquor Ammonii Caustici in 80 c.c. of tap water.

Almost immediately after drenching the animal became paretic, the paresis rapidly progressing to general paralysis. Twenty minutes after drenching a tetanic spasm occurred exactly similar to those described before. After the spasm had passed off, the animal was lying on its side in a state of paralysis, a slight spasm at times jerking the whole body of the animal. The respirations were rapid and shallow and the pulse laboured and accelerated. Later the pulse became very weak and the respirations slow and deep. After the occurrence of the tetanic spasm the animal made continual chewing movements and shortly before death red froth appeared at the nostrils. The animal died two hours after having been drenched.

Post mortem appearances.—Severe emphysema with a fair degree of hyperaemia and slight oedema of the lungs; petechiae in the lungs; hyperaemia

of the trachea which was filled with reddish froth; slight degeneration of the liver; slight hyperaemia of the kidneys; severe hyperaemia of the mucosa of the stomach and duodenum.

Histology.—Congestion and moderate parenchymatous degeneration of the liver and kidneys; marked pneumonic catarrh with alveolar and perivascular haemorrhages; hyperaemia and superficial necrobiosis of the gastric mucous membrane.

Rabbit C (1·75 Kg.) was drenched with 3·0 c.c. Liquor Ammonii Caustici in 80 c.c. of water.

Paresis developed almost immediately after drenching and rapidly progressed to general paralysis. Slight spasms caused the body of the animal to jerk. These spasms increased in severity and 5 minutes after drenching culminated in rapidly repeated tetanic spasms very similar to those described before. The attack of tetanic spasms lasted a few minutes after which the spasms were repeated only at long intervals. During these intervals the animal was lying on its side and the pupils were dilated. Respiration was rapid and shallow and the pulse rapid and laboured. Repeated slight spasms at intervals caused the body to jerk. Later the pulse became weak and occasionally a deep respiratory movement was made. The animal died 1¾ hours after drenching.

Post mortem appearances.—Slight hyperaemia and severe emphysema of the lungs; moderate regressive changes in the liver; slight hyperaemia of the kidneys; very marked hyperaemia of the mucosa of the stomach and small intestine up to the initial part of the jejunum.

Histology.—Moderate parenchymatous degeneration and congestion of the liver and kidneys; very slight fatty changes in the kidney; hyperaemia and oedema of, and sub-pleural and alveolar haemorrhages in, the lungs; hyperaemia and oedema of, and haemorrhages into, the submucosa of the stomach. Other possible changes were obscured by rapid autolysis.

Discussion.

From the information at our disposal it therefore appears that the toxicity of urine, which has been allowed to decompose, is due to ammonia formed from the urea by bacterial action. The toxicity of such urine for animals will depend mainly on the quantity of ammonia present (i.e. the degree of decomposition) and on the pH of the stomach contents of the animal.

The bacteria responsible for the decomposition of the urea are ubiquitous and produce the enzyme urease which effects the decomposition. The optimum pH for the urease action is 7·0-7·38 (Gluscke, 1929).

It is not necessary that urea be broken down *in vitro* to ammonia before becoming toxic, for cases of urea poisoning due to ingestion of urea-fertilizer have been reported by Gluscke (1929) and Steyn (1931). In these cases the symptoms and post mortem appearances closely resemble those described above for ammonia poisoning and poisoning by decomposed urine.

According to Gluscke (1929) urea is broken down (hydrolysed) in the stomach to ammonia and carbon di-oxide according to the equation:—

$$CH_4ON_2 + H_2O = 2NH_3 + CO_2.$$

He has been able to effect the decomposition of urea to ammonia and carbon di-oxide by adding stomach contents as well as grass and hay to solutions of urea. Whether the decomposition in these experiments was due to bacterial action or plant enzymes (some plants are known to contain an urease) he could not definitely say but he suggested that it was due to bacterial action. In his *in vitro* experiments Gluscke (1929) found the decomposition of urea to be very slow, whereas in cases of urea poisoning it is obviously very rapid since animals poisoned by urea exhibit symptoms very soon after ingesting the urea. In such cases the action of urease must be of the same fulminating nature as enzyme action in cases of tympanites. The rapid decomposition of urea in the rumen cannot be wholely explained but it must be remembered, states Gluscke (1929), that the action of urease is favourably influenced by *d*-glucose, *d*-galactose, lactic acid and other substances present in the ruminal contents. Furthermore the buffering action of the ruminal contents will maintain, even if only initially, a pH nearer to the optimum for urease action than would be the case in *in vitro* experiments.

Völtz, quoted by Gluscke (1929), in experiments to replace a portion of the protein in rations by urea, administered 300 gm. of urea daily to a 500 Kg. bovine. The animal exhibited slight ill effects only for the first few days. Gluscke (1929), however, states that very little over 200 gm. of urea will poison a full-grown beast.

Since the decomposition of urea in the rumen takes some time, it is obvious that urea is not as toxic as its equivalent quantity of ammonia if the latter had been formed before ingestion. This is clearly shown by our experiments in which 3·0 litres of fresh human urine had no effect on sheep whereas 3·0 litres of human urine, which had been allowed to decompose, fatally poisoned a sheep in a short time.

Although the toxic dose of urea has not been definitely established, for it would to a great extent depend on the factors which govern the rate of its decomposition in the stomach, it appears that fresh normal urine if consumed in sufficient quantities, may on account of the urea present be toxic. From the literature it appears that urine also contains other poisons in small quantities.

The urine of herbivora contain 2½-3½ per cent. urea, whilst that of carnivora contain 1½ to 3 per cent. and even up to 6 per cent. of urea (Marek, 1936).

ACKNOWLEDGEMENTS.

We wish to thank Mr. H. P. A. de Boom, of the Section of Pathology, for the histological examination of animal organs and Dr. Graf, of the Section of Chemical Pathology, for his interest in this work.

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