THE SYMPTOMS OF URINOD POISONING *

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I. INTRODUCTION

The study of the toxic nature of urine has interested investigators for many years. The continued attraction which this subject affords is no doubt due to the part which urinary retention plays in the vital economy. When it occurs it may produce only headache and a general malaise, yet it cuts down the efficiency to a marked degree. In severer cases it may lead to grave symptoms and even death.

In attempting to account for this poisoning investigators have more often attributed it to a single urinary constituent. But a few have concluded that it was due to a number of substances.

In the study of a new substance¹ which is found in all urines, it was noticed that this substance, called *urinod*, produced headache and malaise. This led to a more careful investigation of its toxic nature.

From experiments conducted thus far, *urinod* seems to be one of the most toxic substances in normal urine. It is thought, therefore, that it may account for some of the symptoms of uremia. It must be understood, however, that this study does not attempt to explain uremia by the aid of *urinod* alone, but merely to show that it may be a contributing factor.

II. PREPARATION OF URINOD

Urine was treated with dilute sulphuric acid so as to make about 3 per cent. concentration of acid. The mixture was permitted to stand several days, becoming darkly colored and giving off disagreeable odors. At this stage the urine was distilled and the distillates were extracted with ether.² Acids, phenols and bases were removed from the ether extract by shaking successively with aqueous solutions of sodium carbonate, sodium hydroxid and hydrochloric acid. The ether solution, containing neutral substances, was concentrated and then subjected to steam distillation to remove *urinod* from the less volatile substances.

The steam distillation gave a low boiling thio-compound, *urinod*, a high boiling compound and sulphur in the distillate. This distillate was extracted with ether. The ether extract was washed with solutions of sodium carbonate, sodium hydroxid, and hydrochloric acid to remove possible traces of acids, phenols and bases. The ether solution was then dried with calcium chlorid and shaken in a separating funnel with metallic mercury to remove sulphur. The ether solution was concentrated and finally distilled in vacuo.

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1. Dehn, W. M., and Hartman, Frank A.: Jour. Am. Chem. Soc., 1914, xxxvi, 2136.

2. For method of extraction see Dehn and Hartman, *loc. cit.*, Note 1, p. 2126.

The first distillate up to about 100 C. at 30 mm. always contained oil, with an allyl mustard oil or ethyl xanthate odor. The middle fraction, boiling at 108 C., with 29 mm. pressure, contained urinod, while the final fraction contained an oil boiling at 170 C. with 29 mm. pressure.

From the first seven hundred liters of distillate from 1,000 liters of urine 5 gm. of urinod were obtained. Of course some was lost during the handling, acidulation, distillation, ether extraction, concentration, treatment with acids and alkalies, distillation with steam, reextraction, drying and distillation in vacuo. It has been estimated that urinod occurs to the extent of one to two parts in 100,000 parts of urine.

III. PROPERTIES OF URINOD

The boiling point of urinod is 108 C. at 28 mm. It cannot be distilled at ordinary pressure without decomposition. Urinod does not solidify in an ordinary freezing mixture. It is a light yellow oil, slightly heavier than water. It is soluble in ordinary organic solvents, but is insoluble in water. It is very volatile with steam. It has a very penetrating, persistent, nauseating odor of urine. It is very toxic, as will be shown in the experiments to follow.

Urinod darkens rapidly in direct sunlight, reduces solutions of potassium permanganate and ammoniacal silver nitrate in the cold, reacts with Millon's reagent, but not with Fehling's reagent. With fixed alkalies the odor of urinod is changed to a terpene-like odor.

IV. COMPOSITION³ AND STRUCTURE OF URINOD

The empirical formula of urinod has been established as C_8H_8O .

Urinod is insoluble in hot dilute solutions of hydrochloric and sulphuric acids; therefore it cannot contain a basic (or alcohol-oxygen or ether-oxygen) group.

Urinod is optically inactive, hence, if not a racemic mixture, it cannot contain an asymmetrical carbon atom.

Urinod reacts with bromin contained in carbon tetrabromid, giving a strong evolution of hydrogen bromid and a solid bromo-derivative; hence it is a *cyclic* compound. Additional evidence of its cyclic nature is obtained from the formation of a dinitro-derivative (golden needles melting at 78 C.) by treatment with cold, dilute nitric acid.

Urinod reacts with semicarbazide, forming a compound melting at 254 C. Therefore it is either a *ketone* or an *aldehyde*.

Urinod reacts with hydroxylamin phenylhydrazin and hydrogen sulphid, forming derivatives not possessing the characteristic odor of urinod. These compounds indicate the presence of a *carbonyl* group in urinod.

The oxidation of urinod by ammoniacal silver nitrate, also by aqueous solutions of potassium permanganate, indicates close relationship with hydrobenzene derivatives.

3. Dehn and Hartman, *loc. cit.*, Note 1, p. 2138.

No known compounds having the same empirical formula as urinod possess the same properties.

From the foregoing considerations and other considerations, discussed in a paper⁴ previously published, two possible structural formulas have been obtained.

That urinod may possess the second formula gathers support from consideration of its characteristic toxic properties and its odor—the isocyanids and other bivalent⁵ carbon compounds being both toxic and malodorous.

V. URINOD OCCURS IN THE CONJUGATED FORM

That urinod does not occur free in fresh, normal urine is concluded from consideration of the following evidence:

1. The odor of urinod is absent from fresh urine.
2. Hydrolysis by fermentation or chemicals develops composite odors containing the odor of urinod.
3. Urinod is very toxic; therefore for physiological reasons it must be rendered harmless by conjugation.
4. Although urinod is easily volatile with steam, each fraction of the distillate from urine and even the heated residue gives off the odor of urinod, hence not only is its formation by hydrolysis difficult, but, *a priori*, it must exist in the conjugated form.
5. Additional support is given to this conclusion from a consideration of the many other conjugated substances in the urine.

VI. METHODS OF ADMINISTERING URINOD

At the beginning of the experimental work with urinod, a method of injection was sought. But for the reason that solvents for urinod are more or less harmful to the body tissues, this method was thought to be rather unsatisfactory.

In a few cases the pure oil was injected intramuscularly, intravenously or subcutaneously. The use of a syringe was found to be too wasteful because of the oil adhering to it; therefore in the cases

4. For more detailed discussion see Dehn and Hartman, *loc. cit.*, p. 2141.

5. Nef: *Ann. d. Chem. (Liebig's)*, 1894, cclxxx, 303; 1895, cclxxxvii, 274; 1897, ccxcviii, 202. Wade: *Jour. Chem. Soc.*, 1902, lxxx, 1596. Lawrie: *Am. Chem. Jour.*, 1906, xxxvi, 487.

of intramuscular and subcutaneous administration the urinod was dropped from an ampoule into an incision in the muscle or skin.

The method used most often in animal experimentation was to drop the urinod into the pharynx. The capillary tube of a weighed ampoule of urinod was broken and the oil forced out by heat. The weight of the ampoule containing the remainder of the urinod together with its broken capillary, subtracted from the original weight, gave the amount of oil used.

In the two experiments on man in which urinod was taken intentionally, an open vial containing a drop of urinod was used. One nostril was held shut, the other was placed in contact with the opening of the vial, so that enough space was left for the inhalation of outside air. In this manner urinod vapor was mingled with the inspired air.

Because of the difficulty in obtaining urinod in any considerable quantity, the use of small animals was necessary in a majority of cases. In the following experiments something less than a total of 300 milligrams was used.

VII. EXPERIMENTAL RESULTS

1. The frog.—Urinod was quite toxic for frogs, one five-hundredth to one eight-hundredth of the body weight being sufficient to produce death in from twenty-five minutes to a few days, depending on the place of injection. Injections in the muscles of the hind leg were least effective, while doses by the mouth were quickest in their action. Death was due to the stopping of respiration.

A number of symptoms developed in the cases in which death did not take place for several hours. Twitchings and dyspnea were followed by convulsions and a high degree of irritability. In the last stages the animal became limp and would not respond to stimulation.

It is an important fact to be borne in mind that the heart was unaffected by urinod. The heart finally ceased beating, due to asphyxia. The reason that it continued so long after the lungs were inactive was no doubt due to respiration through the skin.

Tree frogs were used in the following experiments because of their small size.

A. A frog was given urinod by the mouth in the proportion of 1 part urinod to 460 parts body-weight. The frog jumped about a few times and then remained quiet. After 2.5 minutes the heart beat 100 times per minute; there were two or three jerky inspirations and then a long pause. After five minutes the animal was so weak that he could not sit up; breathing had practically stopped. After seven minutes he would kick very weakly when disturbed; he jerked and twitched much of the time. After ten minutes convulsions occurred. After thirteen minutes the heart had been reduced to 44 beats per minute; at this time tremors passed over the body. The heart continued beating for twelve minutes longer.

In this animal a condition of non-irritability had developed after ten minutes while death occurred in twenty-five minutes. The intermediate symptoms, such as twitchings and convulsions, were scarce and short-lived. Evidently more than the lethal dose had been given.

An examination of the esophagus and stomach showed that a large proportion of the urinod had not been absorbed. This is not surprising considering the insolubility of urinod in water.

B. Another frog was given urinod in the proportion of 1:800 body weight, by dropping the oil into an incision in the abdominal wall. The frog was very frantic at first, jumping about and in various other ways showing his discomfort. After six minutes breathing had become slow and jerky. After sixteen minutes convulsions occurred, preceded by jerking and twitching; his legs were sprawled out and he was so weak that, although responding to very slight stimulation he could barely jerk. After thirty-six minutes the heart beat 72 times per minute; there was congestion of the blood vessels on the abdomen. After fifty minutes there was a quiet period interrupted by occasional jerks and twitches. After 1.75 hours, the heart beats were only reduced to 70 times per minute; the frog was no longer nervous, and breathing had become more spasmodic than ever. After three hours the heart beats were 56 per minute and twitching of individual muscles continued. After 4.5 hours the frog stopped breathing. At 5.5 hours after the administration of urinod the heart stopped beating.

This experiment demonstrates that although urinod is practically insoluble in water it is absorbed in sufficient quantity to affect the respiratory center. Very little, apparently, is necessary to cause dyspnea, as in six minutes this occurred, while it took four and one-half hours to carry enough of the poison to this center to stop its action completely.

As in the preceding case, very little of the urinod given was carried away.

The decrease in the rate of the heart beat is always in proportion to the decrease in the respiration and lags behind, as these experiments and those that follow demonstrate. Moreover, the fact that urinod has no direct action on the frog's heart was shown in another way: Excised frog-hearts were immersed in Ringer's solution, in which a drop of urinod had been placed. The rate of beat was then compared with other hearts in the same conditions except that urinod was absent. With ten trials no effect could be noticed even when urinod was brought in contact with the heart in the form of a large drop.

C. In a third experiment⁶ urinod in the proportion of 1:2,500 body-weight had been injected into the muscles of the thigh of a frog. He immediately showed his irritation by jumping about. (These first effects were undoubtedly due partly to the mechanical irritation in making the incision.) After two minutes he jumped about very frantically, but his efforts were very weak. After three minutes he became very quiet; the injected leg had become paralyzed. After thirteen minutes he frequently gaped his mouth. After eighteen minutes the heart beat 59 times per minute and the muscles occasionally twitched. After twenty-one minutes there were convulsions. After twenty-three minutes his breathing had become irregular and he had become very frantic. This was followed seven minutes later by a state of nonirritability. After thirty-two minutes breathing had all but ceased, muscular twitchings and heart beats being the only indications of life for a time. After thirty-five minutes there were six respirations in one minute, first a single respiration, then a pause of forty seconds, followed by 5 respirations in as many seconds; another pause then a few more respirations followed. The injected leg was by this time congested with blood. Judging by previous experiments, it was thought that these symptoms were ushering in the end. After seventy minutes, however,

6. It is worth while to call attention to the similarity of urinod poisoning to carvone poisoning, as carvone can be easily obtained, while urinod is obtained only after considerable time and labor. The chemical structures and physical properties of the two substances are somewhat similar. Carvone is an unsaturated cyclic ketone with a penetrating odor. It is insoluble in water. Although not so toxic as urinod, carvone produces death in the same manner by injury to the respiratory center. The heart stops beating only after asphyxiation. The preliminary symptoms are twitching and dyspnea, while in grave cases convulsions and conditions of non-irritability follow. These effects were studied in the frog, the lizard and the mouse.

the frog began to recover. After two hours he had apparently recovered. In three days the injected leg was red and swollen to the tip of the toes; the frog had again become quite sick. He died during the third day.

In this experiment it was not positively known whether death was due primarily to urinod or to secondary causes. The last symptoms preceding death were a gradually increasing weakness, with an increasing condition of non-irritability.

2. *The lizard*.—The animals used in these experiments did not belong to a very active species (*Gerrhonotus multicarinatus*).

The symptoms resulting from urinod poisoning resembled those present in the frog, except that there was considerable jerking of the body from side to side. Death was due to a checking of respiration. Urinod was administered orally in all cases.

A. A lizard was given urinod in the proportion of 1:14,000 body-weight. After two minutes the lizard began to jerk his body and twitch his eyelids. Gradually the spasms increased in vigor and breathing became more difficult. In the course of an hour the jerks became weaker. After 1.5 hours the animal lay still except with an occasional twitching. He would not move when stimulated. During the course of three hours, however, this state of nonirritability had gradually passed away, the animal showing complete recovery.

This experiment demonstrates that in urinod poisoning the symptoms may become very severe, even so far as prolonged paralysis; yet they may be followed by complete recovery. As soon as absorption of the poison commences, detoxification probably begins. If urinod does not occur in sufficient quantity, enough of that being absorbed can be rendered harmless so that a fatal poisoning does not result.

B. Urinod was given to another lizard in the proportion of 1:8,200 body-weight. In a little more than two minutes he began to twitch. The twitches gradually grew into jerks. After four minutes he crawled about slowly, jerking continually. After seven minutes he was so frantic that he darted first one way and then the other. After twenty minutes the ability to crawl had been lost, although there was continued jerking from side to side and twitching of the individual muscles. When placed on his back the lizard could not turn over. In the course of three hours he began to regain the use of his limbs. After four hours he had gained enough to right himself when placed on his back. However, he still continued to jerk. After nine hours he had recovered.

This experiment corroborates the results of the preceding one.

C. In a third experiment the dose of urinod was increased in order to study the symptoms leading up to death. One part urinod to 1,800 parts body-weight, was given. After the poison began to affect him the symptoms became very severe in a short time.

At six minutes he had begun to twitch, while in ten minutes the eyes were half shut and he was unable to crawl. He gradually grew weaker until at one hour from the time of administering urinod, the feet were sprawled out with the soles up. After 1.25 hours, the state of nonirritability was complete, twitching being the only sign of life. Death occurred 1.5 hours after urinod was given.

D. In the fourth case the dose of urinod was slightly increased beyond that used in the previous experiment.

Twitching of the eyelids followed a few seconds after administration. Spasms and paroxysmal breathing soon ensued. After ten minutes the limbs were so weak that they could not support the body. At the end of fifteen minutes an oily excretion was defecated. This contained a large amount of urinod. By this time the eyes of the lizard were kept half closed and when picked up the

7. A lizard which was given a lethal dose of the oil carvone excreted a great deal of it six minutes afterward by the intestinal path.

animal was limp. In thirty-five minutes movement was reduced to occasional twitches. Death occurred one hour after administering urinod.

Autopsies of animals killed by urinod have always shown a large amount of the poisonous oil in the stomach and intestines. Apparently there was always an attempt to remove the urinod by the intestinal path. In this experiment a considerable amount of the oil administered was removed from the body in this manner, but enough remained to kill. That death does not occur very rapidly, as with many soluble poisons, is undoubtedly because urinod is absorbed so slowly.

3. *The mouse.*—It was desirable to study the severer symptoms of urinod poisoning in mammals. Therefore, on account of the small amount of the poison required to produce these results, the mouse was used.

A mouse weighing 10.9 gm. was given urinod at intervals of a few hours to a few days, a drop being placed on the tongue.

First dose: 14.2 mg. (Ratio 1:767 body-weight.) The mouse immediately rubbed his snout on the floor of his cage, causing the oil to run out of his mouth. After two minutes he opened and closed his eyes, and then kept them half shut. After three minutes he jumped and twitched. After six minutes slow and difficult breathing developed. After ten minutes he ran about frantically. After twelve minutes he lay as though in a stupor. After fifteen minutes his eyes were open again. After seventeen minutes he ran about chewing things but not eating. In one hour his symptoms became milder. After two hours he twitched his ears continually. After three hours his body still twitched and he did not move even when stimulated in a manner which had previously provoked a response. After thirteen hours he trembled a great deal; his appearance was depressed.

He twitched for twenty-four hours with eyes half shut and breathing labored; he also seemed to be chilly. A few hours after the administration of urinod the fur became so moist from perspiration that the hair was matted as though it had been immersed in water.

Second dose: Six days after the first dose, the same mouse was given 8.2 mg. of urinod (1:1,329 body-weight). The symptoms, as described above, with little variation, again appeared.

Third dose: Eight minutes after the second dose, 10.3 mg. of urinod was given. In four minutes the mouse's eyes were completely shut; he twitched spasmodically. After six minutes he blinked his eyes. After eight minutes he ran frantically back and forth, occasionally rubbing his snout on the cage; his breathing was slow and irregular. After twenty-two minutes he was breathing rapidly again but irregularly; he also jerked his body. At thirty-two minutes there was a slight spasm. At thirty-seven minutes there was another slight spasm. After forty-two minutes he was frantic and possessed a high degree of irritability. After forty-seven minutes he was so irritable that he jumped at the slightest disturbance. At sixty minutes he had convulsions; then intervals of frantic running about with periods of quiet between them continued for several minutes. After nine hours he still trembled.

Fourth dose: Seven days after the first dose, 3 mg. of urinod was given. The mouse became nervous and twitched. This was followed by a period of quiet.

Fifth dose: Thirteen days after the first dose a drop of urinod was given at intervals during the course of thirty minutes until 60 mg. had been taken. (Ratio 1:182). In twenty minutes after the first drop was given the breathing was slow and difficult; the eyes were half shut and the mouse paid no attention to noises. After twenty-seven minutes the eyes were closed and the breathing was not only slow, but very irregular; first, there was a labored respiration, then two or three respirations followed rapidly. At twenty-eight minutes his head sank to the floor and his body jerked. After thirty-seven minutes he passed

into a state of nonirritability, breathing in paroxysms. At forty minutes he had a convulsion. At forty-five minutes convulsions again occurred. After one hour the breathing became more regular. After 3.5 hours the breathing was almost normal, but the body trembled. At 17.75 hours he was continually blinking his eyes, first one and then the other; there was also twitching of the ears. After nineteen hours he occasionally jerked. He kept up the blinking of his eyes until the end of the fourth day. In this movement he always lacked coordination as the eyes were blinking alternately instead of in unison. During this period he kept his eyes partly closed when not in the act of blinking. On the fifth day he had about regained his normal condition.

The symptoms developed in the mouse were muscular twitchings, heightened irritability, apparent drowsiness, labored paroxysmal breathing and dyspnea.

The same proportion of urinod was not as effective in the mouse as in the lizard for it was impossible to place the oil far enough into the throat to prevent removal to the floor of the cage.

4. *Man*.—Although the graver symptoms of urinod poisoning cannot be determined experimentally in man, he serves as an excellent subject for the study of many minor symptoms.

It was while working with urinod in the laboratory that its toxic nature was discovered through the effect produced on breathing its vapors. This was noticed whether working with the pure substance or with the complex distillate from acid-treated urine.

One of the first effects noticed was the intense nausea produced when working over small amounts of urinod. This was almost invariably followed by headache and mental depression. The headache was often occipital in its location.

During periods when I was handling urinod every day for a number of days together, I noticed loss of appetite and a heaviness of the stomach after eating, also constant weariness and frequent periods of drowsiness. Sometimes there was considerable irritability of temper. Occasionally there were marked restlessness and insomnia, although these were usually followed by heavy sleep.

The breathing of urinod from a small vial for ten minutes caused a peculiar sensation in the head, followed by a numbness in the occipital region. It became impossible to concentrate the attention for a time. Headache and depression soon developed. These symptoms, together with irritability of temper lasted for about five days.

At various times when under the influence of urinod I noticed an unusual chilliness. During one period, about three days in length, after I had handled more urinod than usual, I felt a great desire to micturate several times at night although the bladder might be practically empty. The urine gave a burning sensation in its passage. Moreover during this period some itching of the skin occurred. It may be mentioned that after long exposure to urinod, fatigue developed very early upon exertion.

In distilling urinod on one occasion, the stopper to the flask being accidentally removed, I inhaled a considerable quantity of the vapor. In a few seconds I realized a very peculiar, indescribable sensation in both the lumbar and occipital regions, the latter predominating. Shortly after it took effect I felt extremely restless and irritable. This feeling gradually passed off into headache and depression which lasted for a few days.

It was interesting to note the effect of urinod on other individuals. Those who remained for a few minutes in the room where urinod was being used, complained of headache and depression.

One individual inhaled urinod from a vial for five minutes. An extremely nauseating sensation was experienced while breathing the urinod and for some time later. Headache began in a few minutes, with a tendency to sleep. The next day this person was extremely irritable. The effect passed away in about three days.

If one considers the minute trace of urinod which would be taken into the system by inhalation, one can realize how toxic the substance must be to produce the results described.⁸

An important characteristic of this toxic effect is the slowness with which it disappears.

The symptoms commonly shown by urinod poisoning in man are, nausea, headache (more pronounced in the occipital region), mental depression, loss of appetite, heaviness of stomach after meals, constant weariness and drowsiness. The symptoms occasionally developed are, irritability of temper, marked restlessness, insomnia, inability to concentrate the attention, chilliness and desire for frequent micturition.

VIII. THE LETHAL DOSE OF URINOD

The quantity⁹ of urinod necessary to produce the graver symptoms, or even death, is very small, judging from the experiments on animals.

The amount given them was small, but the portion actually absorbed or carried away by the circulation was very minute, as shown by the quantity remaining unabsorbed. In postmortem examination, urinod given by the mouth is largely recovered in the stomach and intestines, while that injected intramuscularly or subcutaneously is found little diminished in that region.

From these facts it is very certain that amounts considerably smaller than 1 part to 800 parts body-weight (frog) would produce death if it were all absorbed in the circulation. Moreover, if other substances that are normally eliminated by the kidneys, accumulated in the blood, the resistance of the tissues would probably be diminished.¹⁰ It is also quite possible that there is an increase in urinod under certain conditions.

8. Later experiments have shown that when all of the inhaled air is made to pass over urinod in the following apparatus only 2.8 mg. are volatilized in thirty minutes. The following arrangement was used: A liter bottle was supplied with dry air from a tower of CaCl_2 and soda lime. A short wide-mouthed vial, containing a weighed quantity of urinod, was supported so that the urinod was about 0.5 cm. below the opening of the exit tube of the bottle. This exit tube was connected with a piece of rubber tubing. The rubber tubing fits closely in one nostril, the other being held shut during inspiration. At expiration the rubber tube was pinched to prevent any back flow of air. In this way the amount of urinod used could be accurately determined.

9. It has been found recently that by dissolving urinod in olive oil it is more toxic when injected subcutaneously. When given thus, one part of urinod to 3,000 parts body-weight is sufficient to kill mice; even then only about one-half to one-third of the oil is absorbed.

10. Cawadias, Alexandre (Compt. rend. Soc. de biol., 1910, lxi, 153) working with blood serum of uremic patients adopted the hypothesis that a physico-chemical modification of the colloids in the serum made an increase in the toxicity of substances accumulating in uremia—the accumulation of potassium salts, ammonium carbonate and urea played a part in this modification of the colloids.

IX. INDICATIONS OF URINOD RETENTION IN THE BODY

Because of the effect which it might have, on account of its toxic nature, it is of interest to note the indications of urinod-retention in the body. Urinod gives the characteristic odor to urine; therefore its presence is recognizable from its odor. Also, urinod is a normal constituent of all urines. If at any time urine does not have an odor, from the above considerations it would be concluded that urinod had been retained in the body. The odor of urine is said to be absent in some cases of uremia,¹¹ therefore, in those cases urinod is probably retained in the body.

Positive evidence of urinod retention is obtained from the fact that the skin and breath of uremic patients are often described as having a urinous odor.¹² This observation and the following would indicate that not only was urinod retained but that it was present in the free condition, as it is the unconjugated substance which gives the urinous odor.

Christison's¹³ observation is very important in its bearing on this point. He found the odor of urine in the heart blood of a man who had died of uremia. Two ounces of blood were removed with great care from the heart so that contamination was impossible. This blood was shaken with alcohol and filtered. Following this it was carefully evaporated to dryness on a vapor bath. The residue was then treated with HNO_3 , giving the odor that is obtained when urine is treated with HNO_3 .

X. A COMPARISON OF URINOD SYMPTOMS WITH UREMIC SYMPTOMS

The symptoms of urinod poisoning, as shown in the foregoing experiments, are headache, nausea, loss of appetite, heaviness of the stomach after meals, twitching, irritability of temper, mental dulness, physical weariness, drowsiness, dyspnea, convulsions and a condition of nonirritability. Occasionally there are other symptoms such as restlessness, insomnia, itching of the skin, frequent micturition, chilliness and fatigue after slight exertion.

Tyson¹⁴ says that a frequent desire to micturate is an early symptom of uremia. In regard to the symptom of chilliness, that was described by Saundby.¹⁵ Fatigue after slight exertion was observed in a case of uremia by Foster.¹⁶ All of the other symptoms of urinod

11. de Beauvais, M.: *Compt. rend. Acad. d. sc.*, 1850, xlvii, 641.

12. Willson: *Jour. Am. Med. Assn.*, 1905, xlv, 23; Porter, W. H.: *Renal Diseases*, 1887, p. 84; Christison, R.: *Granular Degeneration of the Kidneys*, 1839, p. 202.

13. Christison, R.: *Granular Degeneration of the Kidneys*, 1839, p. 169.

14. Tyson, James: *Bright's Disease and Diabetes*, 1881, p. 103.

15. Saundby, Robert: *Lectures on Renal and Urinary Diseases*, 1896, p. 158.

16. Foster, N. B.: *THE ARCHIVES INT. MED.*, 1913, xii, 455.

poisoning are often present in uremia¹⁷ with one exception, and that is the paralysis of the center which coordinates the movement of the eyelids (observed in one instance in the mouse). So far I have not found a description of this symptom in uremia.

An important organ which is affected in uremia is the heart. Urinod has no effect on this so far as experiments up to this time have shown. The changes in blood pressure which sometimes are present in uremia apparently bear no relation to the retention of urinod, as it has been impossible to obtain any effect on blood pressure by the use of urinod.

Apparently urinod plays no part, or at most very little, in the production of dropsy, as only in one instance was there any appearance of edema.

Therefore it is concluded from the above considerations that the symptoms of urinod poisoning resemble very much the nervous symptoms of uremia. It is possible, then, that urinod is the cause of some of the nervous symptoms present in uremia. On the other hand, there are other substances in the urine which produce symptoms such as twitching, convulsions, and a condition of nonirritability and coma. For this reason it is probable that these substances contribute to this effect on the nervous system. A varying amount of these substances which influence the nervous system might account for the variations in uremic symptoms. Obermayer and Popper¹⁸ thought that the changing clinical picture in uremia might be due to the changing power of elimination in the kidney for different substances.

SUMMARY

1. Urinod¹⁹ is prepared from the distillates of acid-treated urines. It is a neutral malodorous oil boiling at 108 C. with 28 mm. pressure. It is a cyclic ketone with the empirical formula C_6H_8O .

2. The symptoms produced by urinod ordinarily are: nausea, headache, loss of appetite, heaviness of the stomach after meals, twitching, irritability of temper, mental dulness, physical weariness, drowsiness, dyspnea, convulsions and a state of nonirritability.

3. Urinod appears to be one of the most toxic substances in urine.

4. Cases are cited in which there have been indications of urinod retention in the body.

5. The symptoms of urinod-poisoning resemble the nervous symptoms of uremia. Urinod retention, therefore, might partly account for these nervous symptoms.

17. Fürbringer, Paul: Diseases of the Kidneys, Trans. by W. H. Gilbert, 1895, i, 38; also Garrod, A. E.: Osler's Modern Medicine, 1909, vi, 91.

18. See Friedrich and Hugo: Ztschr. f. klin. Med., Berl., 1911, lxxii, 332.

19. Further studies are being made on urinod.