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ON

URÆMIC INTOXICATION.

BY

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URÆMIC INTOXICATION.

WHEN we consider how important a part the kidneys fulfil in depurating the blood, we can readily believe that any serious interruption to the due performance of their function must be attended by great disturbance in the healthy action of the other organs of the economy. We find that such is actually the case. Physiological experiments, together with many well-established cases of disease, have taught us that suppression of the urinary excretion is one of the most dangerous events that can happen in the whole range of pathological occurrences.

In the present memoir, I propose to consider the subject of uræmia, or that condition of system due to the accumulation in the blood of matters which in health are removed by the kidneys, basing what I have to say mainly upon my own investigations.

When the renal arteries of an animal—as, for instance, a dog—are ligated, or the kidneys removed, death ensues in from two to four days generally, though occasionally life is retained for a longer period. In one of my own experiments, the animal, a small dog, lived for twelve days; and Marchand[1] mentions a case in which a sheep lived for nearly a fortnight after removal of the organs in question.

At first, the animal upon which this operation has been performed does not appear to be seriously inconvenienced thereby. It eats, sleeps, and follows its other instincts with but little irregularity. After a variable period, noticeable symptoms begin to manifest themselves. These are loss of appetite, nausea, vomiting, and indisposition to exertion of any kind. Occasionally there is purging. Finally, there is either coma or convulsions, or both, and the animal dies in a state of stupor, or in epileptiform convulsions. If, previous to the death of the animal, the blood be examined, it is found loaded with urea, and this substance can generally be detected in the matters vomited and discharged *per anum*. *Post-mortem*

[1] De l'existence de l'urée dans les parties de l'organisme animal autres que l'urine. L'Experience 1839, t. ii. p. 43.

examination reveals the presence of urea in the contents of the stomach, in the blood, the lungs, liver, and other parts of the body.

In Bright's disease, as it affects the human subject, we find that, owing to structural changes in the kidneys, the urine is imperfectly eliminated. An element, albumen, is separated from the blood, which does not normally exist in the urine. The excretion, upon analysis, is found to be deficient in urea, and may even, as I have myself found, be almost entirely free from it. Coma and convulsions at length appear, and death soon follows. If, previously to the above, the blood be analyzed, urea is discovered in large quantity, and a *post-mortem* examination reveals the presence of this substance in nearly every portion of the system. Such is the natural termination of Bright's disease. Sometimes, however, the retained elements of the urine, by their action on the brain and nervous system, produce inflammations of important structures, and death ensues before the stage of uræmic poisoning is reached.

In puerperal eclampsia, in the latter stages of scarlet fever, in yellow fever, and in cholera, symptoms and appearances similar to those above mentioned are frequently present, and probably depend upon a like immediate cause.

To these symptoms, taken collectively, the terms uræmia, uræmic intoxication, and others of like import have been applied.

Various theories have been propounded, relative to the immediate cause of uræmia. Thus, Osborne[1] considered it due to arachnitis; Prevost and Dumas[2] to effusion into the ventricles of the brain; Rees[3] thinks it may be caused by a watery state of the blood; and Bence Jones[4] supposes it to be induced by an accumulation of oxalic acid in this fluid. There is no evidence to support any of these hypotheses; in fact, each has been positively disproved.

The view most generally held, has been that which ascribes uræmia to the direct action of the urea retained in the blood. Later investigations have called the correctness of this hypothesis in question, and much cogent evidence has been adduced against it. Like most other physiological questions, the present is not to be solved but by the patient and thorough research of numerous investigators. I can only hope that the observations and experiments which follow may prove to be contributions in the right direction.

The fact that urea is formed in the blood may be regarded as sufficiently determined. It is not present in the muscles, for analysis fails to detect it; but other substances, the immediate products of their destructive metamor-

[1] On the Nature and Treatment of Dropsical Diseases. London, 1837, p. 36.

[2] Annales de Chimie et de Physique, t. xxiii. p. 90 *et seq.*

[3] On the Nature and Treatment of Diseases of the Kidneys, &c. London, 1850, p. 67.

[4] Lectures on Animal Chemistry. Medical Times, January 3d, 1852.

phosis, and which admit of still further degradation, are found; and the experimental evidence, which establishes the fact that increased muscular exertion leads to increased elimination of urea, indicates these organs as one, at least, of its sources of origin. In addition, we have the beautiful researches of Bechamp,[1] which are conclusive as to its production from proteinaceous substances.

Prevost and Dumas,[2] Marchand,[3] and numerous other observers, have shown that, after extirpation of the kidneys, urea accumulates in the blood, and consequently these organs cannot be regarded as forming this substance. They, in fact, only separate it, as they do the other constituents of the urine, from the blood brought to them by the renal arteries. As the healthy kidneys are constantly in action, urea never normally exists in the blood in any very considerable amount. It is only when, through disease or other cause, the kidneys are prevented performing their function of elimination, or when large quantities are submitted to examination, that urea is to be detected in the blood in any but very small proportion.

The immediate cause of the production of the group of symptoms known as uræmia is at present, as has been already stated, a point upon which there exists some diversity of opinion, though numerous researches have been made with the view of elucidating the subject. Urea has been injected into the blood of animals, and as death did not often follow, this substance has been regarded by some as non-poisonous. Even urine, filtered so as to free it from mucus and epithelium, has, under like circumstances, proved harmless; but when injected unfiltered, death invariably ensued. The inference therefore from these last cited experiments is, that the urine, if not eliminated, is not, as such, capable of causing death, for the mucus and epithelium are not separated from the blood by the kidneys, and consequently are not, properly speaking, constituents of the urine. As, however, the injection of unfiltered urine has always resulted in death, the further deductions must be drawn that epithelium, or mucus, or both, are of themselves poisonous, or that one or both are capable of so acting upon the retained elements of the urine, as to cause the formation of some substance possessed of toxical properties. These conclusions are, however, of course only legitimate, provided that the experiments referred to have been conducted with the care and accuracy so absolutely essential in all physiological investigations. It will be seen hereafter that it is more than probable the experiments cited were not altogether free from error.

In a philosophical treatise on the subject of Bright's disease, Frerichs[4] advances the opinion that uræmia is not due directly to the presence of

[1] Annales de Chim. et de Phys. November, 1856.

[2] Annales de Chim. et de Phys., 1823, t. xxiii. p. 90.

[3] L'Experience, 1839, t. ii. p. 43.

[4] Die Brightsche Nierenkrankheit und deren Behandlung. Braunschweig, 1851, p. 111.

urea in the blood, but to the conversion of this substance into carbonate of ammonia, through the agency of a ferment supposed to be present in the circulating fluid. This view has been accepted by Braun,[1] but has been controverted by Schottin,[2] Zimmerman,[3] Gallois,[4] myself,[5] Bernard,[6] and others.

The arguments relied upon by Frerichs to support his theory are based, mainly, upon experiments on the lower animals—dogs—but partly upon observation of cases of Bright's disease which came under his notice. As this hypothesis, from the source whence it comes, from its apparent simplicity, and from certain facts which seem to give it support, has attracted to a considerable extent the attention of pathologists, I deem it important, before proceeding further, to enter somewhat at length into its consideration.

The fact that urea may be injected into the blood without uræmia following, and that even filtered urine may be thus introduced with impunity, are circumstances considered by Frerichs as incompatible with the hypothesis which ascribes this condition to the retention of the urea *per se*. That in animals, the kidneys of which have been removed, there was vomiting and purging of ammoniacal matters; that ammonia was exhaled from the lungs; and that after death, as well in them as in persons dying of Bright's disease, who during life had manifested symptoms of uræmia, ammonia was discovered in the blood and in the contents of the stomach and intestines; that urea has been frequently found in the blood of persons suffering from Bright's disease, in whom no uræmia was present, and *vice versâ*—constitute, in his opinion, a mass of evidence strongly in favor of the theory he has advanced. Add to all this the results of experiments performed by him with direct reference to the point in question, and we have the main points before us upon which he has constructed the ingenious and beautiful hypothesis, that uræmic intoxication is directly due to the presence of carbonate of ammonia in the blood, which substance has been formed from the retained urea through the action of a ferment. Of the nature of this ferment he does not attempt to furnish an explanation.

Two series of experiments were performed by Frerichs. In the first, a

[1] The Uræmic Convulsions of Pregnancy, Parturition, and Childbed. Edinburgh edition, 1857. Translated by Dr. J. Mathew Duncan, p. 16. I regret that I have not the original work (*Lehrbuch der Geburtshülfe u. s. w. Wien*, 1857) to refer to. Dr. Duncan's translation, however, appears to be very correctly rendered.

[2] Vierordt's Archiv., 1853, Heft 1, p. 170.

[3] British and Foreign Medico-Chirurgical Review. Am. ed., January, 1853, p. 223. From Deutsche Klinik, No. 37.

[4] Comptes Rendus, No. 14, Avril, 1857.

[5] On the Injection of Urea and other substances into the Blood. North American Medico-Chirurgical Review, April, 1858.

[6] Leçons sur les Propriétés Physiologiques et les Alterations Pathologiques des Liquides de l'Organisme, t. ii. Paris, 1859, p. 36.

solution containing from two to three grammes of urea (thirty-one to forty-six grains) was injected into the veins of dogs, the kidneys of which had been previously removed. The animals remained for some hours to all appearance unaffected; a circumstance which Frerichs regards as indicating that the urea, as such, exerted no detrimental influence upon the nervous system. After a longer or shorter period (from one and a quarter to eight hours), the animals became restless, and vomited acid chyme, or a mucous matter of a yellow colour, according as the stomach was full or empty, at the commencement of the experiments. Under the latter condition, the vomited matter was of decided alkaline reaction. Convulsions occurred, and, at the same time, ammonia was expelled with the expired air. Finally, the animals fell into a state of coma, the respiration became stertorous, and death soon followed. Occasionally the convulsions were absent, coma being the first symptom of cerebral disturbance. After death, which generally occurred in from two and a half to ten hours after the injection of the urine, ammonia was always found in the blood. The contents of the stomach, in most instances, gave off a strong ammoniacal odor, and contained carbonate of ammonia in large quantity. In one case they were feebly acid, and even then ammonia was present. This substance was also found in the bile and other secretions.

In the second series of experiments, a solution of carbonate of ammonia was injected into the circulation, the kidneys of the animals remaining intact. Immediately afterwards convulsions ensued, which, in some cases, were very violent, but were soon succeeded by a comatose condition. The respiration was laborious, and the expired air was loaded with ammonia. There was also vomiting of biliary matters. The stupor lasted for several hours; so long as it was present, ammonia continued to be exhaled from the lungs. Gradually it ceased to be expired, and the animals slowly recovered their senses. If, during the coma, an additional amount of carbonate of ammonia was injected, convulsions again occurred, the vomiting was renewed, and the urine and feces were involuntarily evacuated. In from five to six hours, the ammonia again disappeared from the blood, and the animals regained their ordinary liveliness.[1]

There are several objections to be urged against these experiments of Frerichs, and the inferences drawn from them by him and those who coincide with him in his uræmic theory. In order to present these more connectedly and with greater clearness, I quote Frerichs' own details of the first experiment of each series, which may be taken as the type of the others of its class. The first series consisted of six experiments.

"No. 1.—Both kidneys were extirpated from a young full-grown dog, at 3 o'clock P. M., by opening the abdominal cavity. On the following morning, the animal appeared to be perfectly well; it ate, and wagged its tail when spoken

[1] Op. cit., p. 111 *et seq.*

to. The posterior extremities, however, appeared to be paralyzed. At 3 P. M., a solution of two grammes of urea was injected into the left jugular vein. The animal remained in the same state as before, its condition not being altered in the least. At 4 P. M., it became restless, seemed to be choking, and vomited several times. The matter thus ejected consisted of a slimy yellow fluid, with a strong alkaline reaction. Soon afterwards convulsions supervened, the animal rolled from one side to the other. Opisthotonos ensued in the posterior, alternating with violent contractions of the other muscles of the body. From time to time the animal was quiet, after which the convulsions returned with increased violence. In the meanwhile, the vomiting continued, and a glass rod, moistened with chlorhydric acid, and held to the nose, caused the formation of thick white fumes, showing the presence of ammonia in the expired air. By degrees, the convulsions abated in violence, and at length entirely ceased. The animal now lay in a state of sopor, the respiration being quick and difficult. Finally, the respiratory motions became weaker, and at 5½ P. M. death ensued.

"The cavities of the body were immediately opened, and the blood contained in the heart and large vessels collected. It was of a dark violet colour. The colour did not become markedly clear by heating, but by the following morning it had assumed a bright scarlet hue. After four minutes, the fibrin was strongly coagulated. The blood-corpuscles were not changed from the normal form. Ammonia in considerable quantity was contained in the blood—a glass rod previously moistened with chlorhydric acid giving rise to the white fumes indicative of its presence.

"A part of the defibrinated blood was mixed with water, and distilled in the water-bath. A fluid with an alkaline reaction came over, which, being neutralized with chlorhydric acid and evaporated, deposited crystals of chloride of ammonium. To another part of the blood caustic potash was added, and an ammoniacal odour was given off.

"The stomach was strongly contracted, and contained still a few corroded pieces of bone, and a small quantity of a yellow, tenacious, ropy fluid. The stomachal mucous membrane was of a livid red colour, partly through vascular injection and partly through imbibition. The fluid contained in the viscus exhaled a sharp odour of ammonia, reacted strongly alkaline, and formed thick fumes with chlorhydric acid. In an alcoholic extract of the same, no traces of unconverted urea were discovered. In the bile, also, urea was sought for, but only compounds of ammonia were detected. The substance of the brain, and the membranes covering it, contained the normal quantity of blood, and the fluid in the ventricles was not increased in amount. The lungs were healthy, except that posteriorly there was some congestion. The mucous membrane of the trachea and bronchia was slightly reddened. The liver and spleen were, to all appearance, healthy. In the abdominal cavity, a small quantity of bloody fluid was contained. No evidences of intense peritonitis were visible."[1]

The other experiments of this series do not differ in any material respect from the one quoted, except that in the third no ammonia was detected in the expired air. The details of the fifth and sixth are not given.

Now, in these experiments there is not the least evidence that carbonate of ammonia was the cause of death, or even that this substance was present in the blood in any abnormal amount.

In the first place, it is asserted that ammonia was present in the pulmonary exhalation. This statement is doubtless correct, but the inference which Frerichs draws from it is, I think, unwarranted. Ammonia can generally be detected in the products of respiration in healthy dogs, into the veins of which no urea has been introduced, and in which the kidneys

[1] Op. cit., p. 278 *et seq.*

are in healthy functional activity, by employing the test made use of by Frerichs. It is, however, occasionally absent, and in several cases which will hereafter be more specifically referred to, in which urea had been introduced directly into the blood, ammonia was not to be found in the pulmonary exhalation, though recourse was had not only to Frerichs' process, but to others of far greater delicacy.

In the second place, the means employed by Frerichs to establish the existence of ammonia in the blood were faulty in the extreme, and such as will always effect this object if urea be present, even though ammonia, in the first instance, be altogether absent. The defibrinated blood was distilled in a water-bath (at what temperature we are not informed), and an ammoniacal fluid collected. Now, no matter how carefully this operation was conducted, if any urea was present, a portion of it would have undergone decomposition, and ammonia would have appeared in the distillate.

Thus, I took about thirty cubic centimetres of freshly-drawn dog's blood, defibrinated it by shaking it in a bottle with small strips of lead, and then added to it five grammes of urea. It was then placed in a small retort, and carefully distilled in the water-bath at a temperature of 85° Cent. (185° F.), till a sufficient quantity had passed over. A few drops of the distillate were then placed on a strip of glass, and held for a few moments over a vessel containing chlorhydric acid. Upon evaporation, and subsequent microscopical examination, crystals of chloride of ammonium were found in large quantity. A similar strip of glass was then exposed to the vapor of chlorhydric acid, and held for a short time to the ball of the retort whilst the distillation was progressing, in such a manner that the vapour was received upon it. Thick white fumes of chloride of ammonium were produced, and crystals of the same substance were formed upon the glass.

In order further to establish the presence of ammonia, Frerichs added caustic potash to another portion of the blood. This proceeding was equally objectionable as the other, for this substance decomposes urea into carbonate of ammonia, and, of course, therefore it was not surprising that an ammoniacal odour should have been evolved.

Now, I have no intention of denying that ammonia existed in the blood of the dogs submitted by Frerichs to experiment. On the contrary, I believe it to be generally present in the blood of most animals. The fact that Frerichs detected it by holding over the blood a glass rod moistened with chlorhydric acid, is perhaps sufficient to establish the point. But that this circumstance is at all confirmatory of his theory is far from being the case. Richardson[1] has shown, by numerous experiments, that ammonia is a constant constituent of the blood of dogs and many other animals, and by repeated observations I have satisfied myself of the correctness of this

[1] The Cause of the Coagulation of the Blood. Astley Cooper Prize Essay for 1856. London, 1858.

conclusion. I have frequently failed when using Frerichs' test with the glass rod moistened with chlorhydric acid, which, besides its want of extreme delicacy, is liable, from several causes, to yield erroneous results. These, however, with care, may generally be avoided. I have, therefore, preferred either Reuling's[1] process with logwood, or Richardson's, which consists in moistening a slip of glass with chlorhydric acid, and exposing it to the vapour arising from the blood, when, if ammonia be present, minute crystals of chloride of ammonium will be formed, and may be readily perceived under the microscope, with an object glass of moderate power. This process has already been referred to as the means employed during the present researches in examining for ammonia.

I am aware that Davy[2] has not been able to detect ammonia in the blood of the common fowl. Not having access at present to the original paper, I know not what process he employed. With Richardson's method, I have never failed to find it in the blood of this animal in the course of fourteen experiments with reference to this point.

It will be seen, therefore, that ammonia is not an abnormal constituent of the blood, as Frerichs evidently supposes. There is no proof, either, that any of the retained urea was converted whilst in the system into carbonate of ammonia.

The fact that ammonia was found in the contents of the stomach, which consisted of fragments of undigested bone and of mucus, should not have the least weight in the matter, as it is well known that this latter substance causes the decomposition of urea, and the consequent formation of ammonia. No urea was detected in the alcoholic extract of these contents, and it is therefore probable that it was, as Frerichs supposes, entirely decomposed. There is no evidence, however, to lead us to infer that this change was effected in the blood, but, on the contrary, much to warrant us in believing that it took place in the stomach, through the action of the mucus present in this viscus.

In support of this view, I adduce the following experiments :—

Expt. To a full grown dog, fasting, two grammes of urea were administered dissolved in water. Fifteen minutes afterwards, the animal was killed by injecting a solution of woorara under the skin. The stomach was opened, and found to contain nothing but a quantity of thick, tenacious mucus, which exhaled a strong ammoniacal odour. On bringing a glass rod moistened with chlorhydric acid near it, the dense white fumes of chloride of ammonium were formed, and crystals of this substance appeared on a slip of glass used in the manner before specified.

Expt. To another dog, somewhat smaller than the other, five grammes of urea were given in the same manner as before, and at the end of ten

[1] Archiv des Vereins für gemeinschaftliche Arbeiten, Zweiter B. 1856, S. 120.

[2] North American Medico-Chirurgical Review, vol. iv. No. 1, 1860, p. 149. (From Dublin Quarterly Journal of Med. Science, Nov. 1859, p. 425.)

minutes the animal was killed by dividing the medulla oblongata. The stomach was immediately opened. It contained a few fragments of bone, some pieces of undigested meat, and a quantity of thick mucus. The mass was of feeble alkaline reaction, and evolved a barely perceptible ammoniacal odour. The presence of ammonia was further established, as in the first instance.

The contents were then examined for urea by the process hereafter detailed, and this substance was shown to be present in considerable amount. Owing to an accident, it was not weighed.

If, however, the animal has eaten largely a short time previous to the injection of the urea, the change into carbonate of ammonia does not occur, and if the animal be killed soon after the administration of the urea, this substance is found intact in the stomach. If, however, sufficient time has elapsed, it is absorbed into the circulation and excreted by the kidneys.

The following experiments are adduced, as tending to establish these propositions :—

Expt. A full grown dog was fed largely on animal food, and thirty minutes afterwards two grammes of urea were administered to it. Fifteen minutes after taking the urea it was killed by section of the medulla oblongata. The contents of the stomach were of acid reaction. On testing for ammonia by Richardson's method, a negative result was obtained. Neither were fumes of chloride of ammonium formed by the proximity of chlorhydric acid.

Expt. A full grown dog was confined and fed during three days on raw beef, two and a half pounds being given to him in the twenty-four hours. A uniform quantity of water was allowed. The urine of each period of twenty-four hours was collected, and tested for urea by Liebig's process with the nitrate of mercury. On the fourth day, the animal was fed as before, but with each meal two grammes of urea were administered. Six grammes were administered in all. The immediate effect was to increase to a considerable extent the amount of urine eliminated, which contained an augmented quantity of urea. The following table exhibits the results:—

	1st day.	2d day.	3d day.	4th day.
Quantity of urine .	815 c. cm.	795 c. cm.	891 c. cm.	1073 c. cm.
Urea	15.25 gram.	14.75 gram.	15.10 gram.	20.22 gram.

Gallois,[1] from experiments on rabbits, arrived at a similar conclusion, and has also shown that urea acts as a violent poison on these animals when injected into the stomach in sufficiently large amount. A train of symptoms was induced similar to those of uræmia, of which the animals died. During the progress of these symptoms, there was no ammonia in the breath.

I cannot therefore perceive, from a consideration of Frerichs' experiments, and from those performed by myself, as well as from the other evidence adduced, that there are any facts to warrant us in concluding that urea is transformed whilst in the blood into carbonate of ammonia.

[1] Op. cit.

As has been already stated, Frerichs performed another series of experiments, in which the carbonate of ammonia was directly introduced into the blood. In this series, a filtered solution containing from one to two grammes of the carbonate was employed. The first experiment, from which the others do not materially differ, is detailed by Frerichs as follows :—

"No. 1.—Into the jugular vein of a strong, full-grown dog, the solution was very slowly injected. The dog moaned and fell into deep stupor, broken occasionally by convulsions. The respiration was quickened, and the expired air was loaded with ammonia. The coma lasted for three hours, after which the animal regained its ordinary liveliness. During the coma, ineffectual efforts to vomit twice occurred."

The experiments of this series amounted to six in number. None of the animals subjected to them died—a fact which, to say the least, is not one calculated to support Frerichs' hypothesis.

That carbonate of ammonia, when introduced directly into the circulation, produces considerable disturbance in the phenomena of life is doubtless correct. It is, however, excreted so rapidly by the lungs, that the most enormous quantity may be injected without death ensuing. Thus Dr. Steiner,[1] late of the United States Army, performed some years since a series of experiments, some of which show this very strikingly. In one instance, two ounces of strong aqua ammoniæ, diluted with an equal amount of water, were introduced into the circulation of a horse, and although the animal suffered severely for a few minutes, it soon rose from its feet, and trotted about as though nothing had happened.

I have myself[2] also experimented with reference to this point, and have injected as much as sixty grains of carbonate of ammonia into the jugular vein of a dog in normal condition. Convulsions ensued, and ammonia was exhaled from the lungs. The animal, however, recovered perfectly in a short time. Urea was also injected with a like ultimate result. The symptoms observed were, however, by no means identical in both cases.

In a second series of experiments performed, and detailed in the same memoir, the kidneys were removed, and in these animals death followed in a few hours after the injection of ammonia and other substances. From these experiments it is apparent that carbonate of ammonia possesses no pre-eminence as a toxical agent over substances not regarded as poisonous. The investigations, however, are not sufficiently extensive to warrant the formation of decided conclusions from them. It is perceived, however, that when urea was injected it was not decomposed into carbonate of ammonia either in unmutilated dogs or in those deprived of their kidneys.

In Bright's disease, there is a condition of system present very similar to that existing in animals the kidneys of which have been removed. In

[1] Medical Examiner, vol. v. No. 11, N. S., 1849, p. 644.

[2] North American Medico-Chirurgical Review, vol. ii. p. 291.

persons, therefore, suffering from this affection, carbonate of ammonia, if injected in large quantity into the blood, might cause death, or, even if retained in this fluid to any very great extent, the same result might follow. As, however, we have no proof that there is any accumulation of this substance in the blood during the progress of the disease in question, we cannot ascribe uræmic intoxication to its influence.

In the breath of persons labouring under Bright's disease, Frerichs constantly detected ammonia, and this circumstance is advanced as an additional argument in favour of his hypothesis. Allusion has already been made to the fact that ammonia can generally be found in the pulmonary exhalation of dogs. It is perhaps even a more constant constituent of the human breath, even in that of persons who, as far as can be perceived, are in perfect health. Richardson,[1] in many examinations, failed to find it only in one person. Schottin[2] detected it in the breath of persons suffering under other affections than Bright's disease, and in sixteen cases of uræmic poisoning found ammonia in the breath but once, and then, he thinks, it was probably derived from the mouth.

Mettenheimer[3] found white fumes produced by a rod moistened with chlorhydric acid, as readily with the breath of healthy persons as with that of subjects of uræmia ; and, in a note to his memoir, Beneke states that he has arrived at similar results. Viale and Latini,[4] by numerous delicate experiments, have also shown that with each act of expiration ammonia is exhaled from the lungs of the healthy human subject.

From my own investigations, it has resulted that I have scarcely ever failed to find ammonia in my own breath, or in that of very many healthy persons whom I have examined.

I have thus considered, at some length, the arguments and experiments brought forward by Frerichs in support of his theory, and have, I think, sufficiently shown that it is not tenable. It is because, if generally adopted, it may lead to very grave errors in diagnosis and practice, that I have deemed it important to show how many facts tend to disprove the hypothesis in question.

Another view of the cause of uræmia, inferentially supported by Bernard,[5] requires some notice. According to this hypothesis, the condition in question is produced by decomposition of the tissue of the kidneys, and the retention in the blood of the elements arising from their putridity. The

[1] Op. cit.

[2] Vierordt's Archiv. 1853, Heft i. s. 170.

[3] Archiv des Vereins für gemeinschaftliche Arbeiten u. s. w. Band 1, Heft iv. 1854, p. 605.

[4] American Journal of the Medical Sciences, April, 1855, p. 488. From L'Union Médicale, t. viii. No. 98, Août 1854.

[5] Leçons sur les Propriétés Physiologiques et les Alterations Pathologiques des Liquides de l'Organisme. Paris, 1859, t. ii. p. 34 *et seq.*

experiments of Müller and Peipers,[1] and of Marchand,[2] are adduced as tending to establish the correctness of this theory. These observers induced mortification of the kidneys by ligating the renal nerves, and though it is asserted that death ensued from uræmia, it is by no means clear that this condition was not due to the cessation of the function of the kidneys, rather than to the entrance into the blood of septic matters from the mortified organs. Moreover, when the kidneys of an animal are removed, there is certainly no retention in the blood of putrid matters arising from their decomposition, and yet death invariably follows. The entrance into the blood of substances in a state of putrefactive fermentation would more probably induce a pyæmic or typhoid condition of the system than one of uræmia. Finally, in Bright's disease, of which uræmia so frequently forms a prominent concomitant, pathology shows that the existing condition of the kidneys is not one at all analogous to putrefaction.

It is perhaps unnecessary to consider other objections which are applicable to this hypothesis.

The theory which much observation and numerous experiments have led me to think most probably correct, is that which ascribes uræmic intoxication to the direct action of the elements of the urine retained in the blood upon the brain and nervous system, in a manner which we do not at present understand. Of these elements, we have strong reasons for deeming urea the most poisonous.

It is true, that urea has been directly introduced into the circulation of healthy animals without death ensuing. Thus Vauquelin and Segalas[3] injected a solution of this substance into the veins of dogs and cats, without the production of any remarkable effect other than an increase in the amount of urine excreted. They then injected urine, and death followed with symptoms of uræmia. Hence they drew the conclusion, that it is the urine as a whole which, when retained in the blood, induces toxication.

Frerichs[4] thinks that death in these cases arose from the urine being unfiltered; that is, from the mucus and epithelium derived from the urinary passages. He has repeatedly injected from twenty to forty grammes of filtered urine, sometimes even adding urea to it, into the veins of animals, without causing death. An increased quantity of urine was evacuated, but the normal condition of the organism was not otherwise disturbed. A warm saturated solution of urate of soda, likewise produced no untoward result. The amount of urea excreted by the kidneys was, however, greatly increased.

Other observations have also been made relative to the point in question,

[1] Archiv für Physiologie, 1836.

[2] Journal für practische Chemie, Band xi. s. 149.

[3] Journal de Physiologie de Magendie, t. ii. p. 354.

[4] Op. cit., p. 106.

and leading to the same general conclusions. It may therefore be regarded as a well-established fact, that urea, in considerable amount, may be introduced into the blood of healthy animals, without death being necessarily produced.

It has been definitely shown that urea is a normal constituent of the blood. It has been found in the chyle, the lymph, the saliva, the bile, the aqueous and vitreous humours, the perspiration, the liquor amnii, the fluid of blisters, in dropsical effusions, in fecal evacuations, and even in the milk. It cannot therefore be regarded as poisonous, unless when, from defective excretion, it accumulates in the blood.

The amount of urea formed within the organism is, as has already been shown, subject to very great variation; but so long as the kidneys continue to perform the function of elimination in accordance with the requirements of the system, the normal balance between the urea and the blood is not disturbed. Thus it is that urea, and even urine, may be directly introduced into the circulation without inducing continued uræmia; for so soon as these substances reach the kidneys (as Vauquelin and Segalas, Frerichs, and many other investigators have shown), there is an increased elimination of urine, they are expelled from the body, and the coma, convulsions, and other accompaniments of toxication cease.

Occasionally, it happens that when the kidneys do not properly depurate the blood, other organs assume their office, and then uræmic intoxication does not occur.

Several cases are on record in which, from total suppression of the function of the kidneys continuing for a long time, this condition existed. One of the most remarkable of these is that reported to the French Academy of Sciences, several years since, by Monte-Santo,[1] of Padua, the accuracy of whose statements was confirmed by MM. Graefe and Frank from personal observation. In the case in question, there was complete constipation of the bowels and suppression of urine for fourteen years. There was always vomiting in from two to five hours after each meal, and about once a month a large quantity of fecal matter was discharged in the same manner. Although it is stated that there was no odour of urine in these egesta, it is more than probable that the stomach vicariously performed the function of the kidneys, and perhaps the skin also shared with it this office. Some years previously, a case had been reported to the Academy, in which there had been no discharge of feces or urine (by the ordinary channels, at least), for a period of seventy-two years.

Whatever doubt may be attached to such cases as the above, it is very certain that in several diseases it frequently happens that other organs than the kidneys eliminate some of the elements of the urine from the blood. This is especially the case in Bright's disease, in yellow fever, and in cho-

[1] Medico-Chirurgical Review, July, 1833 (American edition), p. 236.

lera. Immediately previous to the accession, and during the continuance of the stage of collapse, in this last named disease, the cutaneous transpiration often contains urea, which is deposited by evaporation on the skin. I have frequently had occasion to notice this circumstance, and in one case in particular, which fell under my charge, the skin of the face, chest, and arms presented the appearance of being dusted with a fine white powder from the large quantity of urea which covered it. The urine contained scarcely a trace of this substance, but it was found both in the fluid vomited and that discharged *per anum*. I do not cite this case as one at all singular, but merely for the bearing which it has upon the subject under consideration. In the numerous cases of cholera which have fallen under my observation, I have generally, whenever an examination was instituted, detected urea in the rice-water discharges from the stomach and bowels.

The experiments of Bernard and Barreswil,[1] which show that when the kidneys are removed from an animal urea is excreted by the gastro-intestinal canal, may also be adduced. These observers extirpated the kidneys from dogs, and found that in those animals which survived but a short time no urea was to be detected in the blood, but that the matters ejected by vomiting and purging contained large quantities of ammonia, the product of the decomposition of the urea through the action of mucus and other gastro-intestinal secretions. If, however, death did not soon follow, the stomach and intestines lost their vicarious office, and then urea was found in the blood.

The fact that urea may occasionally exist in large quantity in the blood without giving rise to uræmic intoxication, is no proof that this substance is not generally poisonous. No one will deny the poisonous properties of arsenic. Dr. Taylor[2] gives the opinion, that a medical witness would be justified in stating it to be fatal in doses of two or three grains, yet subsequently refers to cases in which half an ounce, an ounce and a half, and even two ounces, had been taken without causing death. In the first of these instances, there was not even vomiting. So in relation to opium, as small a quantity as four grains produced death in a robust man, whilst on the other hand, as much as five ounces of laudanum has been taken without even causing sleep. Similar instances might be brought forward in relation to almost every other poisonous substance.

It may perhaps be objected, that in such cases the poisons were not absorbed into the blood; but toxic agents have been introduced directly into the circulation, and like differences in the extent of their action have ensued. I might bring forward numerous examples in support of this asser-

[1] Sur les voies d'elimination de l'urée après l'extirpation des reins. Archives Générales de Médecine, 1847, t. xiii. p. 449. Also, Leçons sur les Liquides de l'Organisme, &c., t. ii. p. 36.

[2] On Poisons. Second American edition, 1859, p. 341.

tion, but it will probably be sufficient to recall the fact of the total insusceptibility of some persons to the action of the vaccine virus.

In Bright's disease, the disorganization of the kidneys is generally of slow progress. They continue to perform their function, though imperfectly, and consequently the amount of urea contained in the blood is not, in the first stages, very excessive. Its accumulation is gradual, and there is therefore time for the system to become in a measure habituated to its presence in such an amount that, if suddenly introduced into the blood and not eliminated, uræmia would in all probability ensue. We find this ability of the system to adapt itself to gradual changes generally present in all animals, and with reference to the action of poisonous substances exceedingly well marked. Thus, by progressively increasing the doses, large quantities of arsenic, opium, strychnia, hydrocyanic acid, and other toxical substances may be taken without the production of the least poisonous effect.

When, however, in Bright's disease, the structure of the kidneys becomes so greatly disorganized as to unfit them entirely for depurating the blood, the elements of the urine continue to accumulate, and if not otherwise excreted, almost invariably give rise to uræmia.

As to the assertion that uræmic intoxication may exist without the accumulation of urea in the blood, I have only to say that there is no evidence whatever to support such a conclusion.

The following investigations were undertaken with the hope of being able to contribute somewhat to a fuller and more exact understanding of the cause of uræmia. I have endeavoured to avoid every source of fallacy, and though (knowing the difficulties which attend researches of this character) I can perhaps scarcely assume to have succeeded, I am, nevertheless, unaware of any circumstances which would invalidate the conclusions drawn.

To say that I entered upon the inquiry without certain preconceived opinions would be far from correct. That such views as I had conceived have, however, blinded me to the truth, or warped my judgment of things as they actually were, I do not believe. Theories are true but for the time being, and physiological hypotheses are even more ephemeral than any others. We should therefore be prepared to yield our convictions without regret, when they do not accord with the results of experiments better devised and more accurate than our own, for only by so doing can we entitle ourselves to be considered useful labourers in the fields of science.

The chemical processes used in the several determinations were as follows :—

In examining the *blood* for urea, a weighed portion was mixed with its volume of strong alcohol, and evaporated over sulphuric acid or chloride of calcium, *in vacuo*, to dryness. The residue was pulverized, and extracted

with cold alcohol. The alcoholic extract was filtered, and carefully evaporated to dryness at a low temperature in the water-bath, and the residue washed repeatedly with small portions of ether. The ether extract was filtered and evaporated to dryness. Nitric acid was then added to the residue, the whole thrown upon a filter of known weight, and subjected to strong pressure. It was then dried at 100° C., and weighed. The difference between the weight of the whole and that of the filter gave the amount of nitrate of urea, and from this the quantity of urea was calculated.

Whenever the amount of urea was too small to determine quantitatively, the dried ether extract last obtained, as in the foregoing process, was placed upon a glass slide, and nitric acid added to it under the microscope. The production of rhombic and hexagonal tablets, the opposite acute angles of which measured 82°, was deemed sufficient evidence of the presence of the substance sought for.

The same methods were used to determine the existence of urea in the vomited and fecal matters, whenever they were examined for it.

For ascertaining the amount of urea in the urine, Liebig's volumetric process with the proto-nitrate of mercury was always employed.

In the determination of ammonia, Richardson's process, already detailed, or Reuling's, was made use of. Whenever negative results were obtained by the one, recourse was always had to the other.

In the first place, I was desirous of ascertaining more definitely than had hitherto been done, the action of urea when injected into the blood of sound and healthy animals.

Expt. A large adult dog, weighing 65 pounds, was fed for three days on fresh meat. During this period, ammonia was constantly found in the breath.

On the fourth day the jugular vein of the left side was opened, and a sufficient quantity of blood abstracted. 100 grammes of this contained 0.019 gramme of urea. Ammonia was present, as it was likewise in the expired air.

The urine passed on this day amounted to 1025 cubic centimetres, and contained 11.28 grammes of urea.

The food was the same as on the preceding days.

On the morning of the fifth day, at 9 A.M., 3 grammes of urea dissolved in 30 cubic cen. of distilled water, were injected into the jugular vein. The animal, from the very first, appeared to suffer pain. It moaned; the breathing became laboured; and it trembled violently, as if from fright or cold. At the end of about 20 minutes, the animal became more quiet, and even appeared to be somewhat stupefied. After nearly an hour had elapsed, convulsions ensued. These were confined almost entirely to the posterior extremities, though at times the other portions of the body were in spasms.

At 10 o'clock, whilst the convulsions were still present, I abstracted 100 grammes of blood. It contained 0.135 grammes of urea. Ammonia was also present, though in no larger amount than on the previous day. Examined microscopically, the red blood-corpuscles were found to be of

normal size, shape, and colour. They appeared, however, to be diminished in quantity. The white corpuscles were very evidently increased in amount.

The animal continued to be convulsed till about 2 o'clock P. M., when coma ensued. This lasted 3½ hours. The dog then awoke, and passed a large quantity of urine. It amounted to 280 cubic centimetres, and contained 2.15 grammes of urea.

Before, during, and after the convulsions, ammonia was exhaled with the breath.

Immediately on the dog awaking, I again abstracted 100 cubic centimetres of blood from the jugular vein. This contained 0.014 of urea.

The total amount of urine voided on this day was 1381 cubic centimetres, containing 14.63 grammes of urea.

The dog ate as much on this day as on any previous one. It recovered perfectly.

Expt. For this experiment, a dog, weighing 38½ pounds, was used. As in the preceding experiment, it was fed for three days on fresh meat. During this period, at only one examination (at 10 o'clock A.M., on the second day), was ammonia detected in the expired air. On the fourth day, 100 grammes of blood were abstracted from the jugular vein, and found to contain 0.027 gramme of urea. Ammonia was also present, and likewise in the pulmonary exhalation.

The urine voided on this day amounted to 834 cubic centimetres, and contained 4.09 grammes of urea.

On the fifth day, at 10 o'clock A. M., 5 grammes of urea dissolved in 30 cubic centimetres of distilled water, were injected into the jugular vein. No immediate effect was produced. After the lapse of 45 minutes, there were slight spasms of the muscles of the eyelids; and 50 minutes after the injection, a severe general convulsion ensued. The vein was now reopened, and 100 grammes of blood taken. Upon analysis, this was found to contain 0.254 grammes of urea. The convulsions continued with great violence for 15 minutes. Coma followed, and lasted till 6 o'clock P. M., when the animal died. There was no excretion of urine after the injection of the urea. The breath was examined every hour for ammonia, but at no time was it detected; neither was it present on this day before the urea was injected. It was, however, found in the blood last drawn. There was neither vomiting nor purging.

Immediately after death the post-mortem examination was commenced.

The substance of the brain appeared to be perfectly healthy; but there was considerable injection of the vessels of the meninges. The ventricles contained about 15 cubic centimetres of serous fluid. Urea was detected in this by the process mentioned, and microscopical examination. It was likewise found in the blood from the sinuses.

The vertebral canal was laid open, and the spinal cord examined. Its substance presented a normal appearance, but there was some congestion of the vessels of its membranes.

The chest contained a small quantity of serous fluid. The lungs were congested, but were otherwise healthy. The heart was of normal size, and did not appear to be in the least diseased. It contained a considerable quantity of fluid blood; 100 grammes were collected from it and the large vessels. The urea in this quantity amounted to 0.873 grammes.

Upon microscopical examination of this blood, the red corpuscles were found to present a crenated margin, and to be in decidedly less than the

normal quantity. The white corpuscles were very much increased in quantity; as much as in well-marked leucocythemia.

The cavity of the peritoneum contained a small quantity of serous liquid. The membrane was in places slightly congested.

The liver was healthy in appearance, but the spleen was considerably enlarged, and contained much more than the normal quantity of blood. The tissue of this latter organ, when examined microscopically, was found to present several important deviations from the normal structure. The Malpighian corpuscles were almost entirely absent, and there was a very great increase in the number of parenchyma cells. These latter were much larger than I have ever found them in the spleen of the dog. The red blood-corpuscles in the splenic blood were generally aggregated in groups, and were of irregular forms.

The stomach was opened, and presented nothing abnormal. The contents, consisting of mucus with a few pieces of bone, were of alkaline reaction, and contained both urea and ammonia, the latter in considerable amount.

The kidneys were enlarged and very much congested. Upon cutting into them, the blood poured out from innumerable orifices. There was no obstruction to either the renal arteries or veins that was discovered after death. The tissue of the kidneys, when submitted to microscopical examination, showed excessive congestion of the capillaries, and enlargement of the Malpighian bodies. Into many of these latter extravasation of blood had taken place, and the tubes were gorged with this fluid.

The bladder contained a small quantity of bloody urine.

Death in this case was, I think, obviously due to non-elimination of urea, and perhaps of the other elements of the urine, through excessive hyperæmia of the kidneys. The cause of the kidney affection I do not know. It was undoubtedly caused either directly or indirectly by the injection of the urea, for up to the time of that operation the function of these organs was perfectly effected.

The experiment cannot but be regarded as exceedingly instructive. There was complete arrest of excretion from the kidneys, and the blood, besides retaining the elements of the urine, received in addition a large quantity of urea, which remained in the organism. In many respects, therefore, the experiment resembled those in which the kidneys have been extirpated, and urea subsequently introduced into the blood. In all such experiments, death has invariably taken place within a few hours. There is, however, this important difference, that the system was saved the shock of a serious operation, and therefore one source of error was eliminated.

In relation to the alteration in the form of the blood-corpuscles, it can scarcely (having Kölliker's experiments in view) be ascribed to the direct physical action of the urea, as the proportion of this substance present in the blood was altogether too small (less than 1%) to effect the change. Kölliker[1] found that a solution containing 30% of urea caused the red cor-

[1] Zeitschrift für wissenschaftliche Zoologie, B. vii. s. 183. Also, Quarterly Journal of Microscopical Science, vol. iii. 1855, p. 289.

puscles of the frog to assume the form of stellate cells, and finally to melt down and disappear. These alterations were also produced, though much more slowly, by solutions of 15% and 12%. When weaker solutions were used, they were not caused. Human blood-cells were only rendered smaller and colourless. The phenomenon observed in the case under consideration, taken in connection with the diminution of the number of red and increase in that of the white corpuscles, must probably be ascribed to some defect in the process of sanguification.

For the purpose of ascertaining the effect of introducing repeated quantities of urea into the blood, I proceeded as follows :—

Expt. A dog weighing forty-eight pounds was fed as the others for three days. Ammonia was always found in the breath.

On the fourth day, at 10 o'clock A. M., one hundred grammes of blood were abstracted, and upon examination found to contain 0.021 grammes of urea. The urine voided during the twenty-four hours amounted to 1224 cubic centimetres, and contained 8.15 grammes of urea. Ammonia was present both in the blood and expired air.

The following morning, at 10 A. M., I introduced into the jugular vein five grammes of urea, dissolved in thirty cubic centimetres of distilled water. No immediate effect was produced, the animal remaining perfectly quiet. At 11.15 convulsions ensued. One hundred grammes of blood were now taken, and yielded 0.193 grammes of urea. The convulsions, at first slight, became more violent. They continued about twenty minutes, and were succeeded by stupor. At 12 M., I injected, as before, five grammes of urea. Immediately afterwards, the animal voided 365 cubic centimetres of urine, in which were contained 3.17 grammes of urea. The coma continued, and at 2 P. M. I again injected five grammes of urea into the blood. At 3.20 P. M. the dog passed 425 cubic centimetres of urine, containing 4.06 grammes of urea. The coma was still present. At 4 P. M., I injected ten grammes of urea, dissolved in thirty-five cubic centimetres of distilled water, into the blood. The stupor was now very profound, the heart beat slowly, and the respiration was laboured and stertorous. I again, at five P. M., abstracted one hundred grammes of blood for examination. It contained 1.683 grammes of urea.

At 5.20, the dog evacuated *per anum* a small quantity of yellow, serous fluid. Urea and ammonia were detected in it.

At 5.45 the animal died, having in eight hours received directly into the blood twenty-five grammes of urea.

Ammonia was found in the breath during the whole course of this experiment, and likewise in the blood.

The urine voided from the commencement to the end of the experiment amounted to 890 cubic centimetres, and contained 7.23 grammes of urea. In the twenty-four hours, there were evacuated 1625 cubic centimetres of urine, in which were contained 12.37 grammes of urea.

On post-mortem examination, the brain and spinal cord were found healthy; the membranes of both were of perfectly normal appearance. About five cubic centimetres of fluid were collected from the ventricles of the former. By simply placing a drop on a glass slide, and adding nitric acid, crystals of nitrate of urea were formed.

The lungs were found congested, but there was no effusion into the pleural cavities. The pericardium was very much congested. The heart contained

a large quantity of blood. Its lining membrane, both in the auricles and ventricles, was redder than natural.

One hundred grammes of the blood from the heart and large vessels contained 1.385 grammes of urea. The blood-corpuscles were of normal size and shape, but, as in the former experiments, were remarkably diminished in number, whilst there was an increase in the number of white corpuscles.

The peritoneal membrane was found congested in patches. The spleen was enlarged, and contained a large quantity of blood. Beyond this the structure, when examined with the microscope, exhibited no abnormal appearance. The kidneys were healthy.

The stomach contained about one hundred and fifty cubic centimetres of fluid, resembling the rice-water discharges of cholera. The intestines also contained a quantity of the same kind of fluid. Both urea and ammonia were present in it.

For the purpose of still further determining the action of large quantities of urea, when introduced into the circulation, the following experiment was performed :—

Expt. A small adult dog, weighing thirty and a quarter pounds, was fed as the others, for three days, on fresh meat, before any investigations were commenced. On the fourth day, at 10 o'clock A. M., one hundred grammes of blood were drawn from the jugular vein. This quantity contained 0.024 grammes of urea. The total amount of urine evacuated during the twenty-four hours was 830 cubic centimetres, containing 5.12 grammes of urea. On this and the preceding days, ammonia was always found in the breath. The food remained the same.

On the fifth day, at 10 A. M., twenty-five grammes of urea, dissolved in thirty cubic centimetres of distilled water (thus forming a nearly saturated solution), were injected into the jugular vein. The animal lay down quietly in its box, and at first did not seem to be greatly disturbed. After a few moments slight twitchings of the muscles ensued, and at 10.30 there was a strong convulsion. Some of the spasms, subsequently, were decidedly tetanic. During the convulsions, I reopened the jugular vein and allowed 100 grammes of blood to flow out. The amount of urea contained therein was 2.005 grammes. The convulsions lasted with undiminished violence till 11.10 A. M., when 481 cubic centimetres of urine, containing 7.50 grammes of urea, were excreted. They then became slighter, and at about 12 M. were succeeded by coma. This continued without intermission till 4.15 P. M., when the animal quietly died in most profound stupor. Two hundred and twenty-five cubic centimetres of urine, containing 3.12 grammes of urea, were excreted a short time before death. There was neither vomiting nor purging. Ammonia was constantly found in the breath, but not in greater quantity than during the previous days.

The blood drawn during the convulsions was examined with the microscope. The red corpuscles were altered in shape, and had become much paler than natural. Scarcely one could be found which was not more or less irregular in outline. They, besides, appeared to have lost their ordinary consistence, and when two or more came together they fused, forming an irregularly formed mass. It was thus impossible to determine microscopically their relative numbers. The white corpuscles were very much increased in quantity. The blood coagulated firmly.

The cavities of the body were opened immediately after death. The

membranes of the brain were found in a state of intense congestion, and the sinuses and large vessels at the base of the cranium were gorged with blood. The substance of the brain, when cut into, exhibited a uniform pink tinge from excess of blood, and the red spots indicating the situation of capillaries were greatly increased in number. This was the first case in which the substance of the brain presented direct evidence of hyperæmia. About twenty cubic centimetres of fluid were collected from the ventricles.

The membranes of the spinal cord were likewise congested, especially in the lumbar region, though more or less throughout their whole extent. Into the cavity of the arachnoid there was an effusion of serous fluid, amounting to fifteen or twenty cubic centimetres.

The lungs were also congested, and there was a considerable amount of bloody fluid effused into the pleural cavities. The pericardium contained a quantity of liquid. The right side of the heart was distended with blood. The left contained but a small quantity. The heart did not exhibit any indications of pre-existing disease of any kind. I was prevented examining the blood chemically. The blood-corpuscles presented the same appearances as those in the blood abstracted before death.

The peritoneum was not diseased; there was no effusion. The liver was of normal appearance. The spleen was enlarged, and contained a large quantity of blood. The red corpuscles were here found almost entirely broken down into a liquid substance. No Malpighian corpuscles were discovered. Large quantities of acicular crystals were scattered through the substance of the spleen, and were visible by microscopical examination.

The kidneys were slightly congested, and some of the tubes contained blood. There were no other appearances of disease.

Two other experiments, similar to the last, were performed. As the results were almost identical, I refrain from detailed descriptions of them.

From the foregoing experiments, it is perceived that there is a limit to the power of the system to eliminate urea, and that when this substance is introduced into the blood in large quantity, it causes death by uræmia. By this I mean that the urea induces such an abnormal condition of the blood, that the brain primarily, and subsequently other organs (the kidneys included), are brought into an abnormal condition, and are thereby prevented performing their functions. From the results of the *post-mortem* examination, it is apparent that this state is one of congestion. I am therefore disposed to think that if the brain had been able to resist the toxic power of the urea for a considerably longer period, the kidneys would have eliminated the surplus urea, and death in these latter experiments would not have ensued.

It is well known that in Bright's disease death frequently occurs from congestions and inflammations of important structures. Thus this termination may be caused by œdema of the glottis, by pericarditis, by pneumonia, by peritonitis, by apoplexy, &c. Have we not reason to regard these several affections as due to an abnormal condition of the brain and nervous system, induced by the retention in the blood of excrementitious matters which in health are removed?

It is, I think, very evident that in neither of the foregoing experiments

was there the least reason to suppose that there was any decomposition of urea into carbonate of ammonia. In the second experiment, this substance was not found in the breath after the injection of the urea into the blood, although it was present at two examinations before this operation.

The alterations in the blood observed with the microscope are very important, and constitute one link in the chain, connecting the retention of urea with derangement of the brain and nervous system. They, perhaps, show that it is not necessary that a toxic condition of the blood should consist altogether in disturbances of the chemical balance existing between its several component parts. The morbid condition of the spleen which was found to exist, is also an interesting circumstance, taken in connection with the changes in the form of the red, and alterations in the relative number of these and the white corpuscles.

Leaving, for the present, the further consideration of these experiments, I proceed to the detail of those constituting the second series, and having relation to the effects following ligature of the renal vessels, or removal of the kidneys.

Exp. A large adult dog, weighing 68¼ pounds, was selected. At 10 A. M. the breath was examined for ammonia, and this substance was found to be exhaled from the lungs in considerable quantity. 100 grammes of blood taken from the jugular vein contained 0.026 gramme of urea.

At 3 P. M. the animal was placed under the influence of chloroform, and the kidneys removed, the abdomen being opened to the smallest possible extent. Scarcely a drop of blood was lost; the anæsthesia passed off without the least untoward effect.

The next morning the dog was in apparently good condition, but manifested no desire to eat, or to move about. At 3 P. M., twenty-four hours after ablation of the kidneys, 100 grammes of blood were drawn, and found to contain 0.083 gramme of urea. The animal refused all food; ammonia was constantly in the breath.

On the third day, at 10 A. M., the dog seemed weaker. Up to this period, however, there had been no convulsion, or coma, neither was there any vomiting or purging. At about 2½ P. M. there was a slight spasm, succeeded in a few moments by a violent general convulsion. At 3 P. M. 100 grammes of blood gave 0.093 gramme of urea. At 4 P. M. the animal vomited a quantity of alkaline mucus, containing both urea and ammonia—the latter in large amount. After the vomiting, the convulsions abated in violence, but soon became as intense as at first. At intervals, however, the animal was free from spasm, and appeared to be also free from pain and uneasiness. At about 8 P. M. coma ensued, alternating with the convulsions till 10½ P. M., when it became persistent, and very profound. Death ensued at about 4 A. M. the next day, sixty-one hours after the removal of the kidneys.

The post-mortem examination of the body was commenced at 9 A. M. The membranes of the brain were intensely congested, and there was an effusion of about twenty-five cubic centimetres of serum into the cavity of the arachnoid. The substance of the brain, when cut into, exhibited a pinkish hue, and numerous bloody points appeared, showing enlargement, and increase in the number of capillaries. The sinuses and vessels at the base of

the brain were turgid. Fifteen cubic centimetres of fluid were found in the ventricles.

The spinal cord was apparently healthy, but its membranes were slightly congested. There was no abnormal amount of fluid found.

Both lungs were congested, and both pleuræ bore evidences of recent incipient inflammation. There was slight effusion. The heart was gorged with blood. The pericardium was healthy. 100 grammes of blood from the heart and large vessels contained 0.097 gramme of urea.

When submitted to microscopical examination, the blood taken from the heart exhibited appearances similar to those previously noticed. The white corpuscles were increased, and the red diminished in number. These latter were also of irregular shape, and decidedly paler than natural.

The peritoneum exhibited traces of recent inflammation; a small amount of bloody serum was found in its cavity.

The spleen was very much enlarged, being at least three times the size of the organ in its normal condition, as noticed when the kidneys were removed. Upon cutting into it, the substance was found entirely disorganized, and of semi-fluid consistence. No traces of Malpighian corpuscles were to be found, and the finer trabeculæ and many of the larger, were entirely detached from their connections. These, with masses of blood-pigment, broken-down corpuscles, a few muscular fibre-cells, and numerous acicular crystals of hæmato-crystallin, were all the morphological elements to be discovered. The parenchyma cells, white corpuscles, free nuclei, &c., had been destroyed.

The liver was also enlarged. It was not examined microscopically.

The stomach, on being opened, exhaled a strong ammoniacal odour. It contained a quantity of yellow, alkaline mucus. Ammonia was present in large quantity, and traces of urea. The intestines contained a like substance.

Exp. At 9 o'clock A. M., 100 grammes of blood were abstracted from the jugular vein of a large dog, weighing 60½ pounds. The urea contained therein amounted to 0.014 gramme. Ammonia was present in the breath. At 1 P. M. the renal arteries were ligated, the animal being under the influence of chloroform. As soon as the anæsthesia passed off sleep ensued, from which the dog did not awake for several hours. At 10 P. M. it appeared to be in good condition, and lapped a little milk. It was quiet, but when spoken to, manifested undoubted signs of intelligence.

The following morning at 8 o'clock the animal was quite lively. It stood up, and even walked a few steps. It ate a little bread and milk. At 4 P. M. it was somewhat drowsy, though it could be easily roused by speaking loudly, or knocking on the side of its box. 100 grammes of blood taken from the jugular vein contained 0.038 of urea. Ammonia was present in the breath. The stupor continued to increase, and at about 8 P. M. was profound. When last seen for the night, at 12 M., the animal was in a very comatose condition.

The next day at 8 A. M., the coma was still present. 100 grammes of blood contained 0.043 gramme of urea. Ammonia was exhaled from the breath, but not to a very abnormal extent. The dog remained in the same condition till about 11½ P. M., when it died, 58½ hours after the ligation of the vessels. There was no vomiting, nor purging, and no visible spasms of any kind.

The following morning, at 9 A. M., I made the post-mortem examination. The membranes of the brain were congested, and about twenty-five

cubic centimetres of fluid were effused into the cavity of the arachnoid. The substance of the brain likewise exhibited evidences of having been in a hyperæmic condition. The ventricles were distended with fluid, which, however, owing to an accident, was not measured. The sinuses and vessels at the base of the cranium were turgid with blood. The spinal cord was not examined.

The pleuræ, the lungs, the pericardium, and heart, were healthy; 100 grammes of blood collected from the latter, contained 0.069 of urea. Examined microscopically, the white corpuscles were found in largely increased quantity, but no other abnormal condition was discovered.

The peritoneum was congested in spots, and exhibited evidences of recent inflammatory action. The spleen was large, and softer than natural. No Malpighian corpuscles could be found. Masses of extravasated blood, in larger quantity than usual, were met with. The liver was not markedly affected. The stomach and intestines contained the residue of undigested food, with some yellow, alkaline mucus. Ammonia and urea were both present.

From the foregoing experiments, it is seen that, after the removal of the kidneys, or ligature of the renal arteries, the amount of urea in the blood was increased threefold within a short period, and that there was no reason to suppose any conversion of this principle into carbonate of ammonia. The pathological changes are interesting, and congestion and inflammation of important organs are seen to be produced as well after ablation of the kidneys, as after the direct injection of urea into the blood, or during the course of Bright's disease. The immediate cause, in each of these instances, is probably the same—derangement of nervous influence through a morbid condition of the blood.

Four other experiments, similar to the two foregoing, were performed. In all, the quantity of urea in the blood was greatly increased after removal of the kidneys, or simple ligature of their arteries, and the post-mortem appearances were in general the same. In three of these there were convulsions and coma, in one coma alone—as in the second experiment of this series. In one experiment, the animal lived forty-nine hours after the operation, in one fifty-three, in one sixty-eight, and in one seventy-three hours. Ammonia was found in the breath both before and after the operation. In none was there any vomiting or purging.

But that these last-mentioned results do sometimes happen, there can be no doubt, and, in fact, judging from the investigations of these observers, they are usual concomitants. In one experiment which I performed subsequently to the above cited, they were present from the first, and doubtless by these means the urea was removed from the blood, and this fluid preserved in a comparatively normal condition. In no other way can we account for the lengthened continuance of life after the kidneys were extirpated. As this experiment is important in several respects, I give the details of it in full.

Expt. A dog weighing thirty-eight pounds was selected for operation.

Before the extirpation of the kidneys, the breath was ascertained to contain ammonia. In 100 grammes of blood were 0.009 grammes of urea.

The kidneys were removed at 9 A. M., the dog being under the influence of chloroform. After the operation, the animal fell into a quiet sleep, and did not awake for six or seven hours. At about 6 P. M. it ate a little bread and milk.

The following morning at 8 o'clock it was in apparent good condition, wagged its tail when spoken to, and ate quite freely of bread and milk. It remained in the same condition all day, manifesting, however, no desire to move out of its box, though it occasionally turned from one side to the other.

The next morning it was found that in the night a little mucus had been vomited. This contained ammonia, but no urea. No other circumstances worthy of note occurred during the day.

On the fourth day, at 7 A. M., the animal seemed somewhat uneasy from nausea. Several efforts to vomit occurred, but nothing was ejected. At about 4 P. M., there was a fecal evacuation of a thin, serous fluid, of a yellow colour. Ammonia was present, but no urea. Crystals of ammonio-magnesian phosphate in large quantities were visible by the microscope. No food was taken on this day.

At 7 o'clock the following morning, it was found that there had been both vomiting and purging of ammoniacal matters during the night. One hundred grammes of blood were abstracted at 9 A. M., and found to contain 0.011 grammes of urea.

On the sixth day, there were both vomiting and purging. The animal was sensible, but refused food.

On the seventh, eighth, and ninth days, vomiting and purging occurred several times. Ammonia and urea were present in each evacuation. On each of these days, a pint of milk was conveyed to the stomach through a tube.

On the tenth day, at about 12½ P. M., a slight convulsion occurred. A pint of milk was injected into the stomach. There was neither vomiting nor purging.

On the eleventh day, at 9½ A. M., another convulsion took place, more violent than the first. The animal was, however, still sensible.

On the twelfth day, at 7 A. M., the dog was found in a comatose condition. One hundred grammes of blood were abstracted at 12 M. This quantity contained 0.041 grammes of urea. The wound in the abdomen had nearly healed. The ligatures on the renal vessels came away. Coma was present during the whole day, and death took place some time in the night after 11 o'clock. The animal was cold the following morning at 7 o'clock.

Thus life had remained for at least 278 hours after the kidneys were extirpated.

Ammonia was detected in the breath on every day but the last.

The post-mortem examination was commenced at about 11 o'clock A. M. The membranes of the brain were apparently healthy, but there was slight sub-arachnoidal effusion. The substance of the brain was of normal appearance. The spinal cord and its membranes were healthy. The lungs were congested, and there were several recent pleuritic adhesions. The pericardium was in several places adherent to the heart. This latter organ was in a state of incipient fatty degeneration. It was full of uncoagulated blood, 100 grammes of which contained 0.046 grammes of urea.

The red corpuscles, both in this blood and in that abstracted on the day of death, were very much diminished in number, whilst the white corpuscles were correspondingly increased. The former were also broken down, and softer than is normally the case.

The peritoneal membrane was congested, and several intestinal adhesions had taken place. The spleen was enlarged, and felt like a bag of water. When the enveloping membranes were cut, the substance flowed out, like molasses in colour and consistence. Examined microscopically, nothing was perceived but shreds of white fibrous tissue, masses of decomposed blood-corpuscles, blood pigment, and large quantities of acicular crystals. The liver was enlarged, and in a state of congestion. The stomach and intestines contained nothing but a little mucus.

It is seen from this experiment that so long as vomiting and purging continued, there was no accumulation of urea in the blood, and no consequent uræmic intoxication. It was only when these ceased that the latter event ensued. It is therefore strongly confirmatory of the conclusion arrived at by MM. Bernard and Barreswil, which has been previously referred to. The connection between the retention of urea in the system and the occurrence of uræmia is so well marked, that it is difficult to deny to these events the relation of cause and effect.

In the third and last series of experiments, the kidneys were removed, and urea or urine, subsequently directly introduced into the blood.

Expt. From the jugular vein of a medium sized dog, 100 grammes of blood were abstracted at 10 o'clock A. M., and found to contain 0.021 grammes of urea. Ammonia was detected in the expired air. At 11 A. M. the animal was placed under the influence of chloroform, and the kidneys removed. At 12 M., five grammes of urea dissolved in thirty cubic centimetres of distilled water, were injected into the jugular vein. No immediately noticeable effect was produced. At 1½ o'clock P. M., convulsions of great violence suddenly ensued. One hundred grammes of blood from the jugular vein yielded 0.042 grammes of urea. A large quantity of highly ammoniacal fluid was vomited. It contained urea. The convulsions continued with undiminished violence till about five o'clock, when coma gradually ensued, and remained present till death, which occurred at about 8 o'clock P. M.

Before death, and during the height of the convulsions and coma, the breath was examined for ammonia, which, although constantly found, was not present in larger qnantity than before the kidneys were removed.

At 7½ o'clock the following morning, the post-mortem examination was commenced.

The membranes and substance of the brain were healthy, but there was a little sub-arachnoidal and ventricular effusion.

The lungs were highly congested, as were also the pleuræ in several places. The pericardium was healthy, and the heart was of normal appearance. It contained a small quantity of uncoagulated blood. One hundred grammes taken from it and the large vessels, yielded 0.032 grammes of urea.

The peritoneum was anteriorly much congested, and there was about one hundred cubic centimetres of bloody serum in its cavity. The spleen

was hyperæmic, and its normal structure disorganized, as in the previous experiments. The liver was not perceptibly diseased.

The stomach and intestines contained a small quantity of alkaline fluid. It was highly ammoniacal. Urea was not detected in it.

Three other experiments, similar to the foregoing, were performed. The results were almost identical, and it is therefore, perhaps, unnecessary to refer to them more in detail.

In the two following experiments, urine was introduced into the blood.

Expt. A dog weighing somewhat less than forty pounds was used for this experiment. The breath examined for ammonia gave distinct evidence of containing it. Previous to removing the kidneys, it was determined that 100 grammes of blood from the jugular vein contained 0.017 grammes of urea.

Anæsthesia was induced by chloroform, and the kidneys extirpated at 9 o'clock A. M. As soon as the insensibility had passed off, one hundred cubic centimetres of fresh urine (voided during the induction of the anæsthesia), unfiltered, were injected carefully into the jugular vein. No immediate effect was produced. At 12 M., thirty cubic centimetres more of the same urine were introduced into the blood. The animal remained quiet in its box till about 2 o'clock P. M., when a slight convulsion ensued, lasting only a few seconds, and confined to the anterior muscles of the body. Shortly afterwards, another occurred more violent than the first. This was followed by others. At about 4 P. M. they ceased, and coma commenced to make its appearance. One hundred grammes of blood from the jugular vein were found to contain 0.030 grammes of urea. The coma continued till after 12 P. M. The dog was found dead the ensuing morning at 5 o'clock. There had been neither vomiting nor purging. Before death, the breath was frequently examined for ammonia, and always with affirmative results.

The post-mortem examination was made at 8½ o'clock A. M. The appearances observed were not materially different from those noticed in the case just detailed, except that the pericardium was congested, and there was some little effusion into its cavity; 100 grammes of blood from the heart and large vessels, contained 0.036 gramme of urea.

Exp. A dog, weighing 49¾ pounds, was the subject of this experiment. Ammonia was found in the expired air; 100 grammes of blood from the jugular vein gave 0.027 gramme of urea. The animal was at 10 A. M. brought under the influence of chloroform, and whilst anæsthesia was present, the kidneys were extirpated. When insensibility had passed off, 100 cubic centimetres of filtered urine—evacuated during the process of inducing anæsthesia—were injected into the jugular vein.

After the expiration of about two hours, convulsions ensued. These at first were slight, but more violent ones soon followed. They lasted till a few minutes before 3 P. M., when coma supervened; 100 grammes of blood taken from the jugular vein were found to contain 0.035 gramme of urea. The coma persisted, and at 8½ P. M. the animal died. There was no vomiting nor purging. Ammonia was found in the breath throughout.

The post-mortem appearances were not essentially different from those observed in the preceding experiment. The contents of the stomach were however acid, and did not contain ammonia.

From the experiments, constituting this last series, it is clearly seen that the introduction of urea, or filtered or unfiltered urine into the circulation of animals deprived of their kidneys, induces death more speedily than if such substances had not been thrown into the blood; for, we have perceived from the experiments of the immediately preceding series, that animals, the kidneys of which have been extirpated, or the renal arteries ligated, live for from forty-nine to 278 hours after the operation; whereas, in the series last detailed, death occurred in from eight to fifteen hours, in a condition of system not to be distinguished from that known as uræmia. Taken, therefore, in connection with the experiments of the first series, in which urea was introduced into the blood of sound animals, and with those of the second, in which, through extirpation of the kidneys, the elements of the urine were retained in the blood, and we have almost demonstrative proof that the resulting uræmia was directly due to the operation of these causes.

Taken as a whole, from an attentive consideration of the foregoing investigations, I think the following conclusions are legitimately deducible:—

1st. That the injection of urea, in limited quantity, into the blood of animals, produces a certain amount of disturbance in the nervous system, similar in its symptoms to the first stages of uræmia, but that this condition even disappears, if the kidneys are capable of so depurating the blood as to eliminate the toxic substance.

2d. That urea, when introduced into the circulation in larger quantity than can in a limited period be excreted by the kidneys, induces death by uræmia.

3d. That by ligature of the renal arteries, or removal of the kidneys, the elements of the urine being retained in the blood, render this fluid unsuitable to the requirements of the organism, and, consequently, induce a condition of system not essentially distinguishable from the uræmic intoxication of Bright's disease, or that caused by the direct introduction of urea into the blood. As, however, was pointed out by Bernard and Barreswil, so long as the urea, or the products of its metamorphosis, are discharged by the stomach or intestines, uræmia does not take place, but, that when these channels become closed, convulsions and coma are produced, and death soon follows.

4th. That the introduction of urea or urine into the circulation of animals, the kidneys of which have been ablated, shortens the life of such animals, as Frerichs and others have already shown.

5th. That there is reason to believe that the urine, as a whole, is more poisonous than a simple solution of urea, for, in those cases in which urine was injected into the blood, the amount of urea thus introduced was much smaller than that previously thrown in, in a pure state, and yet symptoms of as great intensity followed.

6th. That urea, or the elements of the urine, as a whole, induce such a condition of the nervous system, as strongly to predispose to congestion

and inflammation of the viscera, especially the lungs, pericardium, and spleen.

7th. That urea, when directly injected into the blood, or suffered to accumulate in this fluid by extirpation of the kidneys, deranges, in some manner, the process of sanguification, so as to disturb the normal relation of proportion existing between the white and the red corpuscles, and either to hasten the decomposition of these latter, or to interfere with the due removal from the blood of such as are broken down and effete.

8th. That there is no reason to suppose that, under the circumstances specified, urea undergoes conversion into carbonate of ammonia, but that, on the contrary, there is sufficient evidence to warrant the conclusion that no such process ensues. The fact that in the foregoing experiments a larger amount of urea was generally found in the blood taken from the body after death, than in that abstracted during life, is, of itself, conclusive against any such hypothesis.