RECOVERY OF ABSORBED MORPHINE FROM THE URINE, THE BLOOD AND THE TISSUES.

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Historical.—Of all the ordinary poisons there is none that has more frequently been attended with failure to recover it from the body, both in poisoning of the human subject and in experiments on animals, than the alkaloid morphine. These failures have occurred even when the quantity taken or administered was very large, and all the attending circumstances apparently the most favorable for its recovery. Indeed, in the numerous experiments thus far made upon animals, the results have been negative, save in a few instances.

Among the earlier observers, Dr. Christison[1] failed to detect morphine in the contents of the stomach of a young woman who died in five hours after taking two ounces of laudanum; and in another instance the contents of the stomach, withdrawn four hours after two ounces of laudanum had been taken, failed to furnish satisfactory evidence of the presence of the poison.

M. Dublanc[2] sought in vain for morphine in the blood and urine of animals killed by it. And M. Lassaigne[3] could not detect the alkaloid in the blood drawn from a dog twelve hours after thirty-six grains of the acetate were injected into the crural vein; nor, again[4] in the liver or the blood of a dog poisoned with eight ounces of Sydenham's laudanum.

[1] On Poisons, Amer. Ed., p. 537.
[2] Archives Gen., i, 150.
[3] Ann. de Chim. et de Phys., xxv. 102.
[4] Jour. de Chim. Med., 1841, 488.

Orfila[1] failed to find the poison in the blood of three dogs that had been given respectively twelve, fifteen and eighteen grains morphine acetate, and found it in only one instance in the urine.

Bouchardat[2] believed he had found the alkaloid in the urine of a person who had taken .05 gram; and Leforte[3] concluded that it was eliminated by the urine. But the tests relied upon by these observers—iodine in potassium iodide by the former, and iodic acid by the latter—have no positive value.

Dr Taylor[4] mentions two cases, one in his own practice, in each of which one grain of morphine hydrochloride had been taken and death took place in ten and thirteen hours respectively; but no trace of morphine could be detected in the stomach in either case.

Dr. Ebertz[5] failed to find a trace of the poison in any part of the body of a woman who had taken 0.25 gram (nearly four grains) of a salt of morphine and died from its effects within fifty minutes afterward.

Dr. Ogston[6] records a case in which nine or ten grains of morphine hydrochloride caused death within a few hours, and none of the poison had been ejected and no remedy applied. A most searching examination, by himself and Professor Gregory, failed to detect any trace of morphine in the alimentary canal or elsewhere.

In a fatal case of laudanum poisoning recorded by Dr. Tidy,[7] repeated analyses of the contents of the stomach failed to reveal the presence of a trace of either meconic acid or of morphine.

In experiments upon three rabbits, Erdmann[8] found the poison in the first, in the stomach; in the second, only traces in the urine; and in the third, only traces in the blood, none being found in the urine, brain or spinal cord. He concluded that morphine was decomposed in the system.

Cloëtta[9] examined, by Erdmann's method, the urine of a patient who had taken for some time daily six to seven grains morphine acetate, but failed to find a trace of the poison.

In a case of morphine poisoning, Dr. Kreyssig[10] found the poison in the vomited matters by the iron test, but failed to find a trace either in the blood or urine. Prof. Maschka[11] reports a similar case in which none of the poison was found in the stomach.

Prof. L. A. Buchner[12] relates the case of a child quickly killed by three doses of morphine acetate of two grains each, and he failed to find any evidence of morphine either in the contents of the stomach or alimentary canal. And in another case, in which a child quickly died from the effect of extract of poppies, similar negative results were obtained.

[1] Traité des Poisons ou Toxicologie, trois Ed., ii. 58.
[2] Bull. Gen. de Ther., Dec., 1861.
[3] Jour. de Chim., xi. 93, 1861.
[4] On Poisons, London, 1875, 34.
[5] Ann. d' Hyg., 1875, July, 220.
[6] Lectures on Medical Jurisprudence, 1878, 567.
[7] Forensic Medicine, 1877, 376.
[8] Annal. d. Chem. u. Pharm., Bd. 122, 360, 1862.
[9] Virchow's Archiv., xxxv, p. 376, 1866.
[10] Inaugural Dissertation, Leipzig, 1856; quoted by Landsberg.
[11] Prager Vierteljahr., Bd. 66, p. 65, 1860.
[12] Neues Repert. f. Pharm., Bd. 16, p. 43, 1867.

H. Köhler[1] states that the recovery of morphine from bodies by the known methods more frequently fails than succeeds. Prof. Guy[2] remarks that it is now well understood that in cases of poisoning with opium the best methods of analysis will often fail to yield any evidence whatever of the presence of the poison in the contents of the stomach.

Gscheidlen[3] says that morphine injected into the jugular vein of rabbits may be found in the urine; but this may be due to the great amount administered.

Kauzmann[4] found that morphine might be recovered unchanged from the stomach, feces, the blood and urine. He employed the Uslar-Erdmann method.

E. Vogt[5] failed to find morphine in the urine for twenty-four hours of an old man who took daily large quantities of the drug, but he found it in the feces. In like manner, Bornträger[6] failed to find the poison in the urine of a person who took daily 0.5 to 1.0 gram subcutaneously.

Jacques[7] relates the case of a person, sixty years old, who took for five years daily 1.3 grams morphine in solution, and in addition every second day 2.0 grams subcutaneously, yet he failed to find the alkaloid in the urine, but found it in large quantity in the feces collected for three days.

Dr. W. Eliassow[8] examined with negative results the urine of a person who took daily 0.14 gram of a salt of morphine. So, also, R. Burkart[9] failed to find it in the urine of persons who took morphine in large doses; yet on adding directly .002 gram morphine to 50 cc. urine, he readily obtained evidence of its presence.

E. Landsberg[10] injected subcutaneously into three dogs quantities of morphine hydrochloride, varying from 0.2 to 0.4 gram. The urine from these animals failed to show the presence of morphine. In another case 1.0 gram of the morphine salt was injected; the next day 0.5 gram, and on the third day 1.0 gram. Four hours after the last dose the animal was killed, and 170 cc. urine collected. But no morphine was found in this fluid, nor in the brain, medulla oblongata, or in the liver. In another case 2.7 grams of this salt were injected in divided doses over several days; 130 cc. of urine and the blood were then examined, but with negative results. One gram of the salt was administered, in two portions, by the stomach. Again the urine failed to show the presence of the poison, but it was readily obtained from the feces. From these and other experiments Landsberg concluded that morphine undergoes decomposition in the system.

R. Schneider,[11] under the action of Froehde's reagent, found morphine in the urine of three persons who took daily from 0.02–0.36 gram morphine acetate, partly internally and partly by subcutaneous injection.

[1] Schmidt's Jahrb., Bd. 141, p. 21, 1869.
[2] Forensic Medicine, p. 518, 1881.
[3] Arbeiten aus dem Physiol. Laborat., Würzburg, Bd. 32, 1869.
[4] Zeitsch. f. Analyt. Chemie, viii, pp. 103, 243, 1869.
[5] Archiv. der Pharmacie, Bd. 207, p. 23, 1875.
[6] Archiv. der Pharmacie, Bd. 217, p. 119, 1880.
[7] Localisation des Alcaloides dans le Foie. Thèse Bruxelles, 1880; cited by Landsberg.
[8] Inaugural Dissertation, Königsberg, 1882.
[9] Volkmann's Sammlung Klinischen Vorträge, N. 238.
[10] Pflüger's Archiv. f. Physiologie, Bd. 23, p. 425, 1880.
[11] Jahresbericht für Thierchemie, 1884, p. 236.

Dr. J. Donath[1] examined the urine of a patient who had for five years taken large doses of morphine subcutaneously, and during forty-eight hours had employed 0.36 gram of the alkaloid. Two litres of urine collected during the two following days, examined by Landsberg's method, failed to reveal the presence of a trace of morphine. The urine of this patient was examined subsequently a second and a third time, with like negative results. In another case, in which the patient was using subcutaneously 0.75 gram of a morphine salt daily, 1200 cc. of the urine failed to give any positive evidence of the presence of morphine. In a third case, in which 1.5 grams were injected during forty-eight hours, not a trace of morphine was found in 2.5 litres of urine. From these examinations Dr. Donath concludes that morphine entirely disappears in the animal organism, and is not converted into any product that responds to the tests for morphine.

With the cases now cited may be mentioned the results of the writer's[2] own investigations, made some years since, in which the *blood* from eight different cats and dogs poisoned by opium gave little or no evidence whatever of the presence of the poison, save in one instance, in which two grains of morphine and two ounces of laudanum had been administered

METHODS OF ANALYSIS.—In the early history of this subject about the only method known for the recovery of morphine and the alkaloids in general, from complex mixtures and the tissues, consisted in extracting the finely divided solids by water acidulated with acetic acid, evaporating the filtered liquid and extracting the residue with alcohol. In the further purification of the extract, acetate of lead was used to separate foreign organic matter, and the alkaloid was finally precipitated by sodium carbonate.

After this general method M. Lassaigne[3] recovered morphine when the quantity was not less than two grains in eight ounces of the complex mixture.

About the only tests then known for the recognition of morphine were the iron and the nitric and iodic acid tests.

In 1851 Professor Stas,[4] of Brussels, proposed a general method for the recovery of the alkaloids from organic mixtures, based upon the fact that these bodies in the free state are, for the most part, more or less soluble in *ether*. This method consists essentially of first extracting the alkaloid, in the form of a salt, from the complex mixture, by acidulated alcohol, evaporating the alcoholic extract to dryness, dissolving the residue in water, and treating this solution with an alkali to set free the alkaloid. The alkaline liquid is then agitated with several volumes of ether, which will extract the eliminated alkaloid and, on evaporation, leave it in a more or less pure state.

Professor Otto[5] proposed to modify this method by first agitating the acidulated liquid, before the addition of an alkali, with ether for the purpose of removing certain foreign matters. The aqueous liquid, after decanting the ether, is then rendered alkaline and again extracted by ether. This proved to be an important modification of Stas's original method.

[1] Archiv. f. d. ges. Physiologie, Bd. 38, p. 541, 1886.
[2] Micro-Chemistry of Poisons, 1867, 502.
[3] Ann. de Chim. et de Phys., xxv, 102.
[4] Bull. de l'Academie de Médicine, ix, 304.
[5] Ann. Chem. Pharm., 100, 44, 1856.

Although the method of Stas has proved of the greatest importance for the recovery of the alkaloids in general, yet it has only a limited value for the recovery of morphine, since this alkaloid requires about 7000 times its weight of ether for solution. Nor is *chloroform*, as first advised by Rodgers and Girdwood[1] for the recovery of strychnine, well fitted for this purpose, since morphine is about as insoluble in this liquid as in ether.

For the recovery of the alkaloids in general, but more especially for the extraction of morphine, Uslar and Erdmann,[2] in 1861, proposed the use of *amyl alcohol*, in which morphine is rather freely soluble. This liquid being immiscible with water, the principle and method of application is the same as in the process of Stas.

Soon after the introduction of this method for the recovery of morphine, Froehde[3] made the important observation that morphine and its salts in the solid state, when brought in contact with a drop of concentrated sulphuric acid holding a little molybdic acid in solution, gives rise to a beautiful purple or crimson coloration. This reaction has proved of great value for the detection of morphine, since, when properly observed, it is less open to fallacy than most of the other tests, and surpasses them all in delicacy of reaction.

RECOVERY OF MORPHINE BY AMYL ALCOHOL.

In the following examinations in regard to the application of *amyl alcohol* for the extraction and recovery of morphine, Kahlbaum's alcohol was employed. It was apparently perfectly pure, and had a density, as observed by a picnometer, of .811, at 20° C.

Amyl alcohol is about wholly insoluble in water, but a limited quantity of water is dissolved or taken up by the alcohol. If 100 volumes of the alcohol be agitated with 20 volumes of water, after complete separation of the liquids, the alcoholic liquid will measure 109 volumes, the aqueous being reduced to 11 volumes. In other words, under these conditions one volume of water is taken up by 11.11 volumes of the alcohol, with a corresponding increase of volume of the latter liquid.

On digesting excess of finely powdered, pure *morphine* with amyl alcohol at the ordinary temperature for some hours, with frequent agitation, one part of morphine is taken up or dissolved by about 150 parts by weight of the alcohol. Under the action of heat one part of morphine may be dissolved in about 50 parts of the hot liquid. A hot saturated solution of this kind, after cooling and standing one hour, will still contain one part morphine in about 62 parts of the alcohol; after standing twenty hours, one part in about 82 parts of the alcohol. The *salts* of morphine are more or less extracted from their aqueous solution by amyl alcohol, differing in this respect somewhat according to the form of salt present. On dissolving, in the form of a salt, the equivalent of 25 milligrams pure morphine in 5 cc. water, agitating this solution with 25 cc. pure hot amyl

[1] Lancet, London, June, 1856, 718.
[2] Annal. d. Chemie. und Pharmacie, 120, p. 121.
[3] Zeitschr. Anal. Chem., v., p. 214, 1866.

alcohol, then allowing the mixture to stand for twenty hours, the clear amyl alcohol held in solution, of the morphine, as follows:

	Amyl acohol extracted.	Aqueous solution retained.
Morphine, as acetate	8.93 milg.	16.07 milg.
" " sulphate	4.2 "	20.8 "
" " hydrochloride	3.6 "	21.4 "

Under similar conditions, only that 25 cc. of amyl alcohol already saturated with water were employed, the following results were obtained:

	Amyl alcohol extracted.	Aqueous solution retained.
Morphine, as acetate	5.0 milg.	20.0 milg.
" " sulphate	2.8 "	22.2 "
" " hydrochloride	2.5 "	22.5 "

These results indicate that on extracting an aqueous solution of a *salt* of morphine with pure amyl alcohol, a very notable portion of the alkaloid may be taken up by the alcohol; that this proportion may be diminished by first saturating the alcohol with water, and, finally, that a greater proportion of the alkaloid is taken up when in the form of acetate than when present either as sulphate or hydrochloride.

In the extraction of morphine in its free or uncombined state from the urine, by amyl alcohol, the results are more or less interfered with by the large proportion of *urea* taken up by the alcohol.

On digesting excess of finely powdered urea with hot amyl alcohol, and allowing the mixture to stand some hours, it was found that the liquid still held in solution one part of urea in 78.8 parts of the alcohol.

A still more serious interference is the extraction by the alcohol of certain extractive matters of the urine which, having a strong reducing action, may mislead in regard to some of the tests for morphine.

CASES EXAMINED.

CASE I.—A dog, weighing 10 kilos, whose bladder had just been emptied by means of a catheter, was given, Nov. 7th, 1889, 3.0 grams (46 grains) of pure morphine, dissolved by the aid of acetic acid in 10 cc. water, the solution being introduced into the stomach by means of a tube.

Within ten minutes the animal became very drowsy; soon thereafter there was great stupor, but a slight noise would startle the animal. After about one hour there was great weakness or partial paralysis of the hind legs. At the end of twenty-four hours the animal was much better, the weakness of the hind legs having disappeared; but it remained more or less drowsy for fifty hours, when it was killed by being bled to death.

1. URINE—*A*.—Obtained from the animal by catheterization, two hours and forty minutes after administration of the morphine, 12 cc. turbid urine. This was acidulated with hydrochloric acid, and then extracted by agitation with two volumes hot amyl alcohol, which had already been saturated with water. After decanting the alcohol, the aqueous fluid was rendered alkaline by ammonia, and again extracted by two volumes hot amyl alcohol, and finally washed with a fresh portion of the alcohol. The alcohol thus employed was passed through a filter previously moistened with amyl alcohol and evaporated to dryness.

The alcoholic residue was treated with a little acidulated water, the solution filtered, then rendered alkaline by ammonia, and again extracted by hot amyl alcohol. The residue from the evaporation of this alcohol was treated with a little water, a drop of acetic

acid added, the liquid filtered, then concentrated to a small volume. Slight excess of ammonia was now added, and the liquid allowed to evaporate spontaneously.

On applying to this residue the principal tests for morphine, they promptly indicated the presence of a very notable quantity of the alkaloid. After washing out the crystallized urea present with a little cold water, the morphine was obtained partly in the crystalline state. The total quantity of morphine present in the residue was estimated at about four milligrams.

B.—Withdrew by catheter twenty-two hours after administration of the morphine, 160 cc. urine, having a strong alkaline reaction, and which strongly effervesced on addition of hydrochloric acid, due to the presence of ammonium carbonate. Evaporated the urine to 60 cc., cooled and strained. Extracted the strained liquid, while still acid, with about two volumes hot amyl alcohol, previously saturated with water.

The aqueous liquid, after decanting the alcohol, was treated with slight excess of ammonia and extracted by two volumes hot amyl alcohol. This was decanted, filtered, and evaporated to dryness.

Minute portions of the residue thus obtained clearly indicated, by Froehde's reagent and other tests, the presence of morphine in considerable quantity.

The residue was treated with a small quantity of acidulated water, the solution filtered, then rendered alkaline, and again extracted by hot amyl alcohol. The residue from the evaporation of this alcohol was extracted in like manner a third time by amyl alcohol.

The final residue was treated with about 5 cc. water acidulated with acetic acid, and the filtered solution treated with slight excess of ammonia. Very quickly crystals of morphine separated, and there was finally obtained from the solution, after washing with cold water and with ether, 24 milligrams of finely crystallized, nearly colorless, morphine.

It may here be noted that on washing the urea from a residue consisting of morphine, urea and extractive matters, with cold water, the morphine will be dissolved greatly in excess over its solubility in pure water. This excess may sometimes be recovered, in part at least, by concentrating the liquid to a small volume, adding a trace of ammonia, and allowing the mixture to stand in a closed tube for some days or longer; the morphine may then separate in the form of colorless crystals, even from highly-colored liquids.

2. THE BLOOD.—Fifty hours after the administration of the morphine, the dog still being strongly under the influence of the drug, 300 cc. of blood was obtained from the animal. This was treated with 500 cc. strong, ordinary ethyl alcohol, 5 cc. of acetic acid added, and the whole frequently agitated in a strong cylinder during two days. Decanted the liquid, and pulverized the solids in a mortar, returned the mass to the liquid diluted with water to 1000 cc. and moderately heated the mixture. The cooled liquid was strained and the solids washed and preserved for further examination (*B*).

A.—The strained liquid was concentrated, filtered, and finally reduced to 50 cc. It was then rendered alkaline by ammonia, and extracted with twice its volume of pure, hot amyl alcohol. This was separated, filtered and evaporated to dryness; and the residue thus obtained, after solution and filtration, was again extracted by fresh hot amyl alcohol.

The residue from the second amyl alcohol extract, when treated in the usual manner, furnished 14 milligrams morphine, chiefly in the crystalline state, but rather highly colored.

B.—In order to ascertain whether the above albuminous solids still contained a notable quantity of morphine, which might be recovered by a stronger acid, the mass was treated with 500 cc. water and 10 cc. hydrochloric acid, and allowed to stand one day. The mixture was then largely diluted with water and again allowed to stand.

As the mixture was slimy and would not strain, it was about neutralized by sodium hydroxide, then strongly acidulated with acetic acid. The liquid was then strained, concentrated, filtered, and finally reduced to 100 cc.

This, after addition of ammonia, was extracted with hot amyl alcohol; and the residue

obtained on evaporating this liquid extracted a second time by a fresh portion of amyl alcohol.

From the second alcoholic extract, 8.5 milligrams of very nearly pure morphine were obtained.

3. LIVER.—The liver was cut into small shreds, these crushed in a mortar, and extracted at a moderate heat with 500 cc. water strongly acidulated with acetic acid.

The solution thus obtained was filtered, then reduced to 100 cc., rendered alkaline, and extracted with twice its volume of hot amyl alcohol. The residue from this alcohol was extracted a second time, and this in turn a third time, with fresh portions of amyl alcohol.

From the final alcoholic extract, 41 milligrams of essentially pure morphine were obtained.

4. BRAIN.—The brain was removed immediately after the death of the animal. It presented a rather anæmic condition, being free from any signs of congestion.

The organ was crushed in a mortar, and extracted with diluted alcohol strongly acidulated with hydrochloric acid. The final aqueous solution obtained was extracted by amyl alcohol, and the purification by the alcohol repeated a second and third time.

The final residue clearly showed the presence of morphine, but the total quantity present was very minute.

5. STOMACH.—An examination of the contents and scrapings of the stomach, consisting of little else than glairy mucus, showed the presence of morphine in very minute quantity. So far as known, the animal did not vomit, nor did it take any food after the administration of the morphine.

CASE II.—Injected hypodermically into the side of a dog, weight about 10 kilos, 1.0 gram pure morphine, dissolved by acetic acid in 10 cc. water, the bladder of the animal having previously been emptied by means of a catheter. The animal soon showed the ordinary symptoms of the poison, but after some days fully recovered. The urine was withdrawn and examined as follows:

a. Two hours after administration of the morphine, 20 cc. urine of feeble acid reaction was obtained. This was directly neutralized by ammonia and extracted by hot amyl alcohol. This liquid, after filtration and evaporation, left a residue which readily showed the presence of morphine in decided quantity. After a second extraction by amyl alcohol, and further purification, 19 milligrams of nearly colorless crystals of morphine were obtained.

b. Five hours and a half after the injection obtained 40 cc. of slightly alkaline urine. This was reduced to 20 cc. and then extracted by amyl alcohol. The residue from this extraction, when purified as before, furnished 23.8 milligrams crystallized morphine.

c. Twenty-six hours after the injection obtained 80 cc. urine of slightly acid reaction and sp. gr. 1016. This, rendered alkaline by ammonia, was extracted directly by amyl alcohol. The residue obtained from this extract, when further purified, readily showed, under several tests, the presence of morphine, but repeated efforts failed to obtain it in the crystalline state.

d. Twenty-eight hours after the injection obtained 20 cc. urine. From this obtained very satisfactory evidence of the presence of morphine, but only in the amorphous state. The quantity present was obviously much less than in the preceding examination.

e. Seventy-two hours after the injection obtained 60 cc. of urine. This still clearly showed the presence of morphine, but in further diminished quantity.

f. Twenty cc. urine obtained at the end of ninety-six hours still showed under Froehde's reagent the presence of morphine, but beyond this reaction the results were doubtful.

CASE III.—Injected subcutaneously 0.2 gram morphine, in 10 cc. water, into a dog. This was the same animal used in last experiment, but twelve days thereafter. Marked symptoms appeared within ten minutes.

a. Two hours after the injection obtained 28 cc. urine. This was concentrated to 14 cc. and extracted in the usual manner. The final residue readily showed the presence of

morphine, but the alkaloid was not obtained in the crystalline state. Fine crystals of the chromate, however, under the action of potassium chromate, were obtained.

b. Five hours and a half after the injection obtained 50 cc. urine of acid reaction and sp. gr. 1016. This was concentrated to 20 cc. and extracted in the usual manner. The final residue showed the presence of morphine in perhaps somewhat larger quantity than found in the previous examination, but it was obtained only amorphous.

c. From 14 cc. urine withdrawn at the end of twenty-eight hours the final residue, after purification by ether, gave under Froehde's reagent very marked morphine reactions.

CASE IV.—Administered subcutaneously to a dog weighing 14 kilos 0.1 gram morphine, dissolved as acetate in 10 cc. water. Symptoms of the poison soon appeared.

a. Two hours after the injection obtained 14 cc. very turbid, strongly alkaline urine. The final residue from this urine readily indicated, under the action of several tests, the presence of morphine in quite decided quantity.

b. Sixteen cc. urine withdrawn at the end of four and a half hours also showed the presence of the alkaloid in diminished quantity.

c. Fifty-five cc. urine withdrawn at the end of twenty-eight hours distinctly indicated the presence of morphine in very minute quantity.

CASE V.—A man habituated to the use of morphine in large quantity took daily for some time six grains (0.389 gram) morphine sulphate. While taking this quantity the urine passed December 28th, 1889, during twenty-four hours measured 440 cc., was about neutral in reaction and of sp. gr. 1012. For this case I am indebted to my colleague, Professor H. C. Wood.

Two hundred and twenty cc. of the urine, acidulated with acetic acid, were concentrated to 75 cc., rendered alkaline by ammonia and extracted with about two volumes hot amyl alcohol. The residue obtained on the evaporation of the alcohol readily showed the presence of morphine. After further purification the residue, under the action of several tests, indicated the presence of morphine in very marked quantity, the reactions being about as well-marked as with the pure alkaloid, but repeated attempts failed to obtain it in the form of well-defined crystals.

CASE VI.—A man affected with polyuria, accustomed for some years to the use of large quantities of crude opium, was at the time of this examination taking daily 60 grains (3.9 grams) of the drug in twenty-grain doses three times a day.

The urine voided during twenty-four hours, January 4th, 1890, measured 4040 cc., had a distinctly alkaline reaction, and sp. gr. 1007.

One thousand cc. of the urine reduced to 100 cc. and extracted with amyl alcohol in the usual manner furnished, under the various tests, very satisfactory evidence of the presence of morphine in quite notable quantity.

An attempt was made to also ascertain the presence of meconic acid, but on account of the presence of the phosphates and other interfering substances the results were not satisfactory.

CASE VII.—Dr. W. H. Price, of the University Hospital, kindly furnished me the following case. A coachman, aged 50, greatly depressed in spirits swallowed, February 13th, 1890, a fluid ounce of ordinary laudanum. When seen by Dr. J. Daland, thirty-five minutes afterward, the patient was in a comatose state; the pupils were contracted to a point and the respirations four per minute.

Under the use of strychnine and atropine hypodermically, electricity and other active measures, at the end of thirty hours the patient was quite himself again.

Eight hours after the poison had been taken about 250 cc. urine was withdrawn from the bladder by catheterization; 160 cc. of this urine, reduced to 75 cc., was extracted by amyl alcohol; and this extract purified by a second, and then a third, extraction by the alcohol, and finally by ether.

The final residue, when examined by Froehde's, Husemann's, the nitric acid, and iron tests, very clearly showed the presence of morphine. The urine in this case was not examined until the third day after its withdrawal.

CASE VIII.—A man, with suicidal intent, took at 10 P. M., March 10th, 1890, ten fluid-

drachms of laudanum. When seen ten hours thereafter by Dr. J. Daland, who kindly furnished me the particulars of the case, the patient was in a state of great stupor, from which he could be partially aroused. Under moderate treatment he soon recovered. The first urine voided by the patient was lost.

About twenty hours after the poison had been taken 120 cc. of very turbid urine, of slightly acid reaction and sp. gr. 1022, was collected. This, after addition of acetic acid, was filtered, then reduced to 50 cc. and extracted in the usual manner by hot amyl alcohol.

The residue obtained on evaporating the alcohol was extracted by ether, and this liquid allowed to evaporate spontaneously. The ether residue very clearly showed the presence of morphine, but only in very minute quantity.

It should be added that the only evidence that ten drachms of laudanum had been taken in this case is the statement of the patient himself; nor is anything known in regard to the quality of the drug taken.

CASE IX.—A gentleman on retiring at night took, by way of experiment, a pellet containing ¼ grain (16 milg.) morphine sulphate. The following morning he voided 185 cc. urine, of light color and slightly acid reaction.

This, after concentration, was extracted by amyl alcohol in the usual manner. The residue from this alcohol was again extracted by the alcohol, and the operation repeated a third time with a fresh portion of the alcohol.

The residue from the third alcohol extract, when examined by Froehde's reagent, promptly gave a coloration very similar at least to that of morphine, but the results were not fully satisfactory. Other portions of the residue very promptly reduced solutions of iodic acid and of potassium ferricyanide; but, under the conditions, these reactions have no positive value.

A urine extract of this kind, even in the absence of morphine, will frequently yield, with Froehde's reagent, a coloration which might be mistaken for that of a minute quantity of morphine, due to the reduction of the molybdenum compound. Moreover, this reducing action may entirely prevent or mask the normal reaction of morphine, even when the alkaloid is added to the residue in very notable quantity, as we have seen in repeated experiments.

For the purification of a mixture or residue of this kind, it may be treated with a little water and a drop of acetic acid. The liquid is then filtered, and, while still acid, extracted with several volumes of pure, strong ether.

The ether being decanted, the aqueous liquid is again covered with several volumes of fresh ether, and a drop of ammonia, or sufficient to neutralize the acid, added. The mixture is then quickly and thoroughly agitated. The ether will now take up any morphine present, in part at least, and at most only a trace of urea, if present, the extractive matters and greater portion of urea being retained by the aqueous fluid. The ether is then decanted and allowed to evaporate spontaneously. Since morphine is only very sparingly soluble in ether, this method of purification is applicable only for the recovery of minute quantities of the alkaloid.

The above residue, from the third amyl alcohol extract, when extracted by ether after the foregoing method, gave a very minute, about colorless, residue, which when examined in several portions by Froehde's reagent, gave purple colorations which seemed to leave no doubt of the presence of morphine.

CASE X.—This was a repetition of the foregoing case, only that ⅛ grain morphine sulphate was taken, and the next morning 350 cc. urine, of faintly acid reaction and sp. gr. 1012, was obtained.

After concentration, the urine was extracted by amyl alcohol and finally by ether, in the same manner as in the previous case.

The very minute, final ether residue, when examined in three or four portions by Froehde's reagent, gave well-marked purplish or violet colorations. These results were quite in contrast with those obtained by the reagent from an exceedingly minute residue obtained in the same manner from urine known to be free from morphine.

GENERAL CONSIDERATIONS.

In the use of amyl alcohol for the extraction of morphine from the urine, the *urea* taken up with the morphine interferes more or less with the purification of the alkaloid. In a residue consisting of a mixture of this kind, the urea, as such, may, as we have found, be decomposed by heating the mixture in an air oven for a few hours at 135° C., without any appreciable loss of the morphine. But the presence of the products of the decomposition of the urea prove about as objectionable as that of the urea itself. Since urea is freely soluble in water, whilst morphine is only sparingly soluble, it might be inferred that these substances could thus be readily separated. This is true in regard to pure mixtures, and also when the morphine has assumed the crystalline state ; but when present in only minute quantity the alkaloid seems to be so closely adherent with the urea and coloring matter that these substances are largely dissolved together.

Some experiments were made in regard to the adaptability of *isobutyl alcohol* for the extraction of morphine from complex mixtures, especially from the urine. For this purpose, Schuchardt's alcohol, apparently pure, was employed. If a small quantity of this alcohol be agitated with large excess of water, it is dissolved by the water in the proportion of one volume of the alcohol in about 10.5 volumes of water, as generally stated by writers.

If, however, equal volumes of the alcohol and water, say 100 volumes of each, be mixed and agitated, after repose the alcoholic liquid will measure 103 volumes, the aqueous fluid being reduced to 97 volumes—that is, 100 volumes of the alcohol will take up 3 volumes of water. On treating excess of finely powdered morphine with hot isobutyl alcohol, and allowing the mixture to stand sixteen hours, it was found that one part of morphine was held in solution by 110 parts by weight of the alcohol. Under the same conditions one part of urea was retained in solution by 49.8 parts by weight of the alcohol.

It would thus appear, that morphine, while rather freely soluble in isobutyl alcohol, is slightly less soluble in this liquid than in amyl alcohol ; whereas, urea, on the other hand, is somewhat more freely soluble in isobutyl alcohol than in amyl alcohol.