Original Articles.

HEMATOPORPHYRINURIA, WITH THE REPORT OF A CASE.*

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HEMATOPORPHYRIN is a coloring matter which is derived from the blood, and only rarely forms an important constituent of the urine.

The earliest observations bearing upon this subject were made in 1871, when Hoppe-Seyler¹ found that if hematin was treated with concentrated sulphuric acid, and heat applied, there resulted a compound whose acid and alkaline solutions showed spectral bands unlike any substance he had seen before. Further experiments convinced him that he was dealing with a new compound, to which he gave the name "hematoporphyrin." He forthwith made an effort to determine its chemical composition, arriving at results which were, several years later (1884), found to be incorrect by Nencki and Sieber² who ascertained that its exact chemical formula was $C_{10}H_{18}N_2O_8$.

Nencki³ found that the only chemical difference between hematin and hematoporphyrin was that the latter was hematin free from iron.

In 1874 Baumstark⁴ described two pigments which he obtained from the urine of a case of leprosy, and to which he gave the names "urorubrohematin" and "urofuscohematin." The acid solutions of the former gave a spectrum having a very close resemblance to acid hematoporphyrin, but the alkaline solutions of this substance failed to yield spectral bands like those of alkaline hematoporphyrin. At that time he called attention to the close resemblance of urorubrohematin to iron-free hematin, but did not regard the two substances identical.

In 1880 MacMunn⁵ described a pigment which he obtained from the urine of a case of acute rheumatism, to which he gave the name "urohematin." This pigment was found to yield spectral bands which closely resembled hematoporphyrin. Three years later⁶ (1883) he reported other cases of acute rheumatism whose urine presented this peculiar coloring matter. In a paper⁷ published in 1885 he changed the name of this pigment to "urohematoporphyrin."

Neusser⁸ (1881) described a pigment which he found in the urines of two patients, one of whom was suffering from phthisis pulmonalis, and the other from pleurisy with effusion. This pigment was spectroscopically identical with hematoporphyrin.

Le Nobel⁹ (1887) confirmed MacMunn's observations of the occurrence of a pigment in rheumatic fever, and added that he had met with it in pneumonia and cirrhosis of the liver.

In 1889 Stokvis¹⁰ described a coloring matter which he had found in the urine of a woman who had taken sulphonal.

Ranking and Partington¹¹ (1890) reported two cases, both females, who showed obscure nervous symptoms. No sulphonal had been taken. The urine of both cases had a deep red color, and contained hematoporphyrin.

In the same year von Horley¹² described two cases

of hematoporphyrinuria, and in both instances sulphonal had been ingested.

Salkowski¹³ (1891) reported in detail the chemical and spectral examinations of dark red urines of three patients all of whom had taken sulphonal.

In 1892 Hammersten,¹⁴ Goldstein,¹⁵ Sobernheim,¹⁶ and Quinke¹⁷ reported cases of hematoporphyrinuria following the use of sulphonal. Some of these had taken the drug in large doses for some period, while others had taken only a comparatively small quantity.

Herting¹⁸ (1894) described the urine of a case which had taken both trional and tetronal. It had a dark red color and contained hematoporphyrin.

In the same year Schultz¹⁹ reported a case of severe melancholia, in which evening doses of one-half to one and one-half grammes of trional had been taken for four weeks—a total of 25 grammes. The urine passed during the fourth week had a muddy, reddish-brown appearance, in which the chemical and spectroscopical examination showed hematoporphyrin. A few days later the patient died. There was some question as to whether the trional was the direct cause of death.

Müller,²⁰ Hearder²¹ and others have observed this unusual coloring matter following the ingestion of sulphonal, and all records show that more than a single dose (one gramme) of the drug had been taken before the coloring matter appeared.

Nakurai²² (1897) reported the results of 250 examinations of the urine of 144 patients. Hematoporphyrin was found in only ten cases, namely, in all of the six cases of lead-poisoning examined, two out of four cases of intestinal tuberculosis, one out of seventeen cases of rheumatism, and once in a case of empyema following the use of sulphonal. The method employed for the separation of this coloring matter from the urine was that of Salkowski. (See below.)

According to Stokvis,²³ hematoporphyrin has also been observed following an intestinal hemorrhage. He succeeded in producing an artificial hematoporphyrinuria in rabbits and dogs by giving them sulphonal (0.4 to 0.6 gramme per kilo). He found that the sulphonal, apparently by its irritative action, produced a marked hyperemia and frequently small hemorrhages into the mucous membrane of the stomach and intestines. From the hemorrhagic areas he was able to extract a coloring matter which, by the spectroscope, was shown to be hematoporphyrin. He also found this pigment in the urine of rabbits which had been fed upon fresh meat. His conclusion was that the blood which had entered the digestive tract was first changed to hematoporphyrin, then absorbed and eliminated in the urine as such.

Stokvis²⁴ claims that very small amounts of hematoporphyrin can be found in the highly concentrated urine of any healthy person.

Garrod²⁵ found traces of this pigment in the urines of twenty healthy persons. It was constantly present for a considerable period but in varying quantities. His observations were confirmed by those of Hopkins.²⁶

Salkowski's Method²⁷ for the Separation of Hematoporphyrin from the Urine.—"Take about 30 c. c. of urine, add baryta mixture (equal parts of a ten-per-cent. solution of barium chloride and a saturated solution of barium hydrate), until it is completely precipitated. Wash once with water, and once with absolute alcohol, using the latter drop by drop. Transfer the precipitate to an evaporating dish, add six to eight

* This paper will appear in the Medical and Surgical Reports of the Boston City Hospital for 1898. An abstract of it was read before the Boston Society of Medical Sciences, February 16, 1897.

drops of concentrated hydrochloric acid and sufficient absolute alcohol to make a thin pap, then stir thoroughly. Heat over a water-bath, then filter through a dry filter paper, and add sufficient absolute alcohol to make from eight to ten cubic centimetres of filtrate."

This solution (acid) may be examined directly with the spectroscope for the bands of acid hematoporphyrin, or may be rendered alkaline, preferably with ammoniac hydrate, and examined for the characteristic bands of alkaline hematoporphyrin.

It is worthy of note that this alcoholic solution containing the pigment readily decomposes, so that the spectral examinations must be made within a period of two to three days.

Spectrum.—The *acid* alcoholic solution shows two absorption bands: one rather dark, situated between Fraunhofer's lines C and D, with its right border on D; and the second, sharply defined, nearly intermediate between D and E. The *alkaline* solution presents a four-banded spectrum as follows: A faint and very narrow band about midway between C and D; two between D and E, one with its left border covering D, the other nearer E; and the fourth band, which is the darkest of all, but which, however, is not well defined, includes about four-fifths of the space between *b* and F nearer to *b*.

1. Acid Hematoporphyrin.
2. Alkaline Hematoporphyrin.

H. G., female, aged thirty-eight, single, having contracted diphtheria, was admitted to the South Department of the Boston City Hospital on November 25, 1896, under the care of Dr. J. H. McCollom.

Her mother and one sister had died of heart disease. She had acute rheumatism at the age of twenty-one (seventeen years ago), at which time a mitral disease of the heart developed.

In the next thirteen years there were four recurrent attacks of rheumatism, which, with the heart disease, required almost constant treatment. She was quite well in the two years previous to the present attack of diphtheria, excepting for palpitation and dyspnea on exertion.

She had a nervous temperament, and was at times hysterical, having had six or eight hysterical convulsions (eight years ago), following a cessation of the menses. The physical examination showed the heart to be much enlarged, and the presence of a thrill over the precordia. There was a systolic murmur at the apex, transmitted a short distance toward the axilla. There was also a presystolic murmur which was faint but distinct.

Lungs and liver were negative. The abdomen was tympanitic, lax and quite tender. The extremities were edematous.

There was a diphtheritic membrane on both tonsils. A culture from the throat showed the presence of the

Klebs-Löffler bacillus. The patient was given anti-toxin, and gradually improved, although convalescence was very slow, probably because of the extensive heart disease.

About two weeks later (December 10th) she began to have diarrhea and vomiting, which persisted. Soon after this she complained of pain and tenderness in the legs, which, on examination, was found to be confined to the areas along the nerve trunks.

Urine (December 22d): high; strongly acid; specific gravity 1,022; albumin, the slightest possible trace; bile and sugar absent. Sediment: a few finely granular and hyaline casts, some with renal epithelium adherent. Considerable squamous and scaly epithelium, few leucocytes, and an occasional normal blood globule. The urine chart showed the twenty-four-hour quantity to vary between 450 and 600 c. c.

On December 15th the patient was discharged from the South Department and admitted to the wards of the main hospital on the service of Dr. G. B. Shattuck, and later that of Dr. C. F. Withington.

About this time she began to lose sensation in the legs; this was followed (two weeks later) with almost complete loss of sensation up to the waist line, accompanied by involuntary micturition and dejections. The pain on pressure over the nerve trunks was extreme. Patellar reflexes diminished, but present. General muscular atrophy. Diarrhea persistent; frequent attacks of vomiting. Free, and at times, profuse perspiration.

On or about February 10th the urine was found to be very scanty in amount, but on account of the involuntary micturition it could not be collected. On February 12th, however, a small catheter specimen was obtained which had the following characteristics: Color, very dark, resembling port wine; specific gravity, 1.025; reaction, strongly acid; uropheins and indoxyl much increased; chlorides and phosphates much diminished; urea, 3.15 per cent.; albumin, a very slight trace (heat test); bile and sugar absent. The sediment was abundant in quantity, and consisted of a deposit of amorphous urates and a few uric-acid crystals. Some squamous epithelium and a few pus corpuscles. An occasional brown granular cast, and rarely a blood globule. A little fat found adherent to an occasional cast.

No more urine could be obtained, in fact very little was secreted. The patient gradually lost strength, and died on the morning of February 14th. An autopsy could not be obtained.

The treatment consisted chiefly of heart tonics, such as tincture digitalis, tincture strophanthus, strychnine, etc. Bismuth and salol were from time to time given for the diarrhea, but none within four weeks of the time of death. At two different times (January 31st and February 6th) 15-grain doses of trional were given for insomnia.

The dark red urine which was collected on February 12th was examined with the spectroscope. At first, the untreated urine (acid) was used, but with unsatisfactory results, since the two spectral bands of acid hematoporphyrin could not be made out with certainty. The pigment was then separated from the urine by Salkowski's method (see above), and it was found that both the acid and alkaline solutions gave the characteristic absorption bands of hematoporphyrin.

The trional which had been taken was probably the cause of the unusual pigment in the urine of this case,

although there is some doubt: first of all, on account of the length of time which elapsed (eleven and five days respectively) between the ingestion of the drug and the discovery of the hematoporphyrin in the urine; and, secondly, the inability to collect and carefully examine the urine after the trional had been taken.

Whether the disease of the nervous system, and the marked gastro-intestinal disturbance in the case had any bearing upon the cause of the hematoporphyrinuria is not known, although such a possibility exists.

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COMPLETE CONGENITAL OCCLUSION OF THE POSTERIOR NARES: REPORT OF A CASE.¹

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THIS condition is one of such rarity, judging from the literature of the subject, that it might at first seem of little practical interest to the physician; and yet there is no doubt that infants may die from the want of knowledge on the part of the family doctor of the possibility of the existence of such an abnormality. Apart, however, from any practical value which the report of such a case may have, it is certainly interesting in showing how an individual may grow up and live for years in comparative health, to all intents and purposes, without a nose, the respiratory function of that organ devolving entirely upon the mouth.

In a very thorough paper published in 1886, Hubbell gives a *résumé* of all the cases of congenital occlusion of the nostrils, unilateral, bilateral and partial, which had been reported up to that time, making seventeen in all. Of these, occlusion was complete in both nostrils in eight cases, complete in the right nostril in four, left in three. It was incomplete in both nostrils in one case, and in the left in one. The occlusion was bony in twelve cases, membranous in five.

¹ Read before the Boston Society for Medical Improvement, November 15, 1897.

Since 1886 I can find but three cases of complete bilateral occlusion reported. A. Schwendt, of Basle, published a monograph on this subject in 1890. I have been unable to obtain the original article, and the references to which I had access did not mention the number of his cases in which the occlusion was complete. Cases of unilateral occlusion by a bony or membranous septum are more common. Cases also occur in which the occluding septum is only partial in one or both nostrils. But as these two classes offer no important special conditions for consideration, I shall refer only to those cases in which the occlusion was complete in both nostrils, which seem to form a distinct group because of the more serious symptoms which they present.

The following are brief abstracts of reported cases in which the nasal occlusion was complete. Those before 1886 were taken from Hubbell's paper, although the original articles were also consulted in almost every case.

The first case which appears in literature is that of Emmert, which was seen by him in 1851. The patient was a boy, seven years of age, who had been unable to breathe through his nose from birth. He was nourished with difficulty in infancy. Both choanæ were entirely occluded by a bony wall. Mucus and tears constantly discharged from the nose. The sense of smell was absent. The obstruction was penetrated with a special trochar and the openings enlarged with a catheter. Tubes were worn in the nose at times for six months. It was not ascertained in what manner or from what bones the partition arose. The father had syphilis of the pharynx. As nothing is said of the hearing, it is presumed that both it and the condition of the ears were fairly normal.

Luschka's case, reported in 1859, was a female infant who died shortly after birth. The posterior nares were occluded by a bony plate extending upwards and backwards from the horizontal plate of the palate bone to the lower surface of the sphenoid.

Bitôt discovered in a fetus of seven months the nasal foræ imperforate posteriorly, the obstruction being due to the presence of two triangular bones of more or less regular shape, articulating above with the sphenoid, below with the os quadratum or the horizontal plate of the palate bone. Exteriorly their borders corresponded with those of the internal wings of the pterygoid apophysis, while internally they infringed one upon the other and formed a median fissure.

J. Solis-Cohen's case was an infant which had difficulty in sucking and breathing. This was relieved by boring through the occluding structures with a knife and steel probe.

Ronaldson's case, an infant with complete membranous obstruction of both posterior nares and no other abnormality, died soon after birth.

Wilkerson reports the case of a child six years old, who was hand-fed as an infant, being unable to nurse. The senses of smell and taste were very deficient. Both nasal cavities were obstructed at their posterior ends. The obstruction was partially removed by a (special) revolving trochar and canula. The bony plates appeared to be about a quarter of an inch thick. Tubes were worn for six days, then bougies were passed. Nasal respiration was established. No deafness was noted.

Schrötter's case (1884) resembles mine in many ways. The patient was a girl of nineteen years, strong