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BIBLIOGRAPHIC REVIEW

JACQUES PERSONNE

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ABSTRACT

Jacques Personne (1816-1880) was a French chemist who investigated in detail the action of chloral hydrate on the animal economy and believed to have proved that the released chloroform acted as common chloroform in producing anesthesia. For this purpose, he carried additional experiments using pyrogallol instead of chloral. He also explained the use of turpentine as an antidote in phosphorus poisoning. Personne also demonstrated that amorphous red phosphorus was innocuous to the animal economy, that the fermentation of citric acetate produced acetic and butyric acid that the quinine eliminated by the urine had undergone no alteration by its passage through the economy; and that a large amount of the quinine ingested was completely destroyed within the economy.

Keywords: chloral; citric acid, coffee, lupulin; pyrogallol; red phosphorus, quinine; turpentine.

RESUMEN

Jacques Personne (1816-1880) fue un químico francés que investigó en detalle la acción del hidrato de cloral en la economía animal y se creyó haber demostrado que el cloroformo liberado actuaba como cloroformo común en la producción de anestesia. Para ello, realizó experimentos adicionales utilizando pirogalol en lugar de cloral. También explicó el uso de la trementina como antídoto en la intoxicación por fósforo. Personne también demostró que el fósforo rojo amorfo era inocuo para la economía animal, que la fermentación del acetato cítrico producía ácido acético y butírico, que la quinina eliminada por la orina no había sufrido alteración por su paso por la economía; y que una gran cantidad de quinina ingerida fue completamente destruida dentro de la economía.

Palabras clave: ácido cítrico; café; cloral; fósforo rojo, lupulin, pirogalol; quinina; trementina

INTRODUCTION

Life and career (Personne, 1870, 1874; Méhu, 1880; Jungfleish, 1881; Villiers, 1904; Goris, 1920; Courtois, 1980; Berman, 2022)

Jacques Personne was born on October 17, 1816, in Saulieu (Côte-d'Or, France), the eldest of the three children of Jeanne Ducharne and Léonard Personne, a baker and operator of a limekiln he had constructed by himself. During his basic education Jacques did not distinguish himself for diligence and interest in his studies. For these reasons, when he ended it in 1833, at the age of 16, his father obtained for him a position of apprentice in the pharmacy of his cousin Etienne Vaudrey in Saulieu. This was a three-year program of practical studies leading to the degree of pharmacist of second class, the lowest level in the professsion. At the end of his training, Jacques decided to improve his position and become a first-class pharmacist, a rank that would give him the authority of opening his own pharmacy, if so desired. For this reason, in December 1835 he moved to Paris and enrolled in the École Supérieure de Pharmacie in Paris and began working in the pharmacy of Defert to maintain himself. In 1837, during Jacques' stay in Paris, his father died in a tragic accident: while working on the roof of his limekiln, the ceiling crumbled, killing him.

In 1839, Personne competed successfully for an internship in a Parisian hospital pharmacy entering the framework of the public assistance service, where he would stay until his death, shortly before reaching the age of retirement. In 1842, he published with Deville, a fellow intern, his first paper about milky blood serum, where they concluded that this matter was very similar to human fat (Personne & Deville, 1842). Another paper followed devoted to determining the amount of lead present in 13 samples of orange blossom water samples taken from different retailers during their annual visits to the École de Pharmacie (Personne, 1844).

Jacques served as chief pharmacist in three Paris municipal hospitals: Midi (1849–1857), Pitié (1857–1878), and La Charité (1878–1880). In 1843 he served as préparateur of chemistry and physics for Antoine Bussy (1794-1882) at the École Supérieure de Pharmacie, and then of chemistry and toxicology (1847). In 1854 he received his degree of pharmacist of first class, after presenting a thesis on the chemistry and biology of lupulin (the glandular hairs of the hop) (Personne, 1854a).

Between 1865-1868, Personne served as head of practical work, pharmaceutical work, and chemical and pharmaceutical work at the École Supérieure de Pharmacie. In 1877 at the age of sixty-one, Personne earned his doctoral degree after successfully defending a thesis about the chemistry of chloral (Personne, 1877). Jules Jamin (1818-1886), Henri Sainte-Claire Deville (1818-1881), and Louis Joseph Troost (1825-1911) were the judges. This delayed achievement probably was the reason for his not being elected to the Académie des Sciences. In the same year Personne was appointed instructor of a newly established course in analytical chemistry in the École Supérieure de Pharmacie. In 1895, this course became the chair of analytical chemistry.

In 1875 Personne was admitted to the Academy of Medicine. In 1878 he became a member of the Council on Public Hygiene and Health of the department of the Seine. The Société de Pharmacie awarded him twice a Grand Prix (gold medal and 1500 francs), one for his work about alcoholic tinctures (Personne, 1845), which eventually was adopted by the French Codex, and the second, for his memoir about the chancre (competition of the Société; *J. Pharm., 31*, 46-47, 1857). The Académie des Sciences awarded him the Barbier Prize for his work about chloral.

Personne passed away suddenly in Paris, on December 11, 1880.

SCIENTIFIC CONTRIBUTION

Personne wrote about 30 papers about inorganic chemistry, analytical chemistry, organic chemistry, and physiology. As customary to a candidate for a scientific academy, he published a booklet describing his research and achievements (Personne, 1870, 1874). In addition to the few subjects described below, he determined the amount of lead present in orange blossom water (Personne, 1844); the presence of iodine in certain aquatic plants (Personne, 1850); the chemistry and biology of lupulin (Personne, 1854abc); the combinations of iodine and tin (Personne, 1862a); the reduction of ferric chloride by heat (Personne, 1862b); the volumetric dosage of mercury (Personne, 1863); the chemistry of starch iodide (Personne, 1880); the chemistry of potassium silicate (Personne, 1900) and of manganic and permanganic acids (Personne, & l'Hermite, 1851); etc.

In what follows, care must be taken of the fact that Personne used the old nomenclature and the value of the atomic masses.

Fermentation of citric acid

Personne wrote that certain manufacturers of citric acid had tried to improve the economics of the process by utilizing the lemons grown in foreign countries, which went without use in large quantities. Their basic idea was to use their juice to manufacture calcium citrate and bring the salt to France, where it would be split with sulfuric acid. Unfortunately, this scheme had failed: this calcium citrate arrived always modified in such a form that it never produced citric acid. The producers had noted that the mass contained a large percentage of calcium carbonate and assumed that this compound had originated from the calcium citrate (Personne, 1853, 1870). According to Personne, the composition of citric acid, $C_{12}H_8O_{14}$ (using the old values of atomic masses; today $C_8H_8O_7$), could hardly justify this decomposition. It was hard to justify how such a complex structure would split only into CO_2. It had to be assumed that the production of this gas was accompanied by other compounds, yet to be identified. These facts led Personne to investigate this phenomenon in more detail (Personne, 1863).

For this purpose, Personne carried the following experiments. He filtered the lemon juice, neutralized it with calcium carbonate, and introduced the slurry in a flask provided with an apparatus for collecting gases, keeping everything at 30° to 35°C. After a day or two, he noticed the evolution of a gas that continued until all the citrates had transformed. A second experiment, carried with raw juice, showed the same process, but at a much faster rate, accompanied by a faster release of gas. A third experiment carried with pure citric acid mixed with a small amount of brewer' yeast, proceeded even faster. In all the experiments, the calcium citrate was seen to disappear slowly while the liquor released the unpleasant odor of butyric fermentation. The liberated gas was always composed of CO_2 and hydrogen, mixed with a variable amount of water (Personne, 1853).

The resulting liquid was filtered and concentrated by evaporation. It always left a white residue of a mamelonated calcium salt, apparently not crystallized, which dissolved easily in water. This salt was decomposed by silver nitrate, giving an abundant white precipitate, which disappeared almost completely on washing with hot water. Evaporation of the wash water left a residue of fine needles, looking like silver acetate. The remaining solid was dried completely under sulfuric acid (Personne, 1853).

The precipitate remaining after washing, and the salt obtained crystallized from these waters, were examined separately after complete drying over sulfuric acid. The first was found to contain 56.13% of the silver and the second, 62.75%. These compositions were very similar to those of silver butyrate and acetate, respectively. Apparently the precipitates appeared to be mixtures of butyrate with a little acetate, and acetate with a little butyrate. Personne separated the two acids by fractional distillation. Eventually he obtained a two-layer liquid, oily in appearance, resembling a volatile fatty acid, and possessing the mixed odor of acetic and butyric acids. Subjected to distillation, it passed a fraction boiling up to 150 °C and having the pungent and penetrating odor of acetic acid. The other fraction passed at 160 °C and had the distinct odor of butyric acid (actual boiling point: 163.5 °C); it dissolved like it in water, and the excess swimmed to the surface of the aqueous solution. This acid was tested as its silver salt, which was found to contain about 55% silver, a number which agreed perfectly with the composition of silver butyrate. All the above results indicated that calcium citrate was transformed, by a real fermentation, into acetic acid, butyric acid, CO_2, and hydrogen, as indicated by the following equation (Personne, 1853)

$$\underset{\text{citric acid}}{4(C_{12}H_8O_{14})} + 4HO = \underset{\text{butyric acid}}{2(C_8H_8O_4)} + \underset{\text{acetic acid}}{3(C_4H_4O_4)} + 20CO_2 + H_8 \quad \text{(old atomic masses)} \qquad (1)$$

According to Personne, the constant presence of hydrogen in the products of the transformation of citric acid suggested that the splitting of the acid actually took place in two stages, first into acetic acid and lactic acid:

$$\underset{\text{citric acid}}{4(C_{12}H_8O_{14})} + 4HO = \underset{\text{acetic acid}}{3(C_4H_4O_4)} + \underset{\text{lactic acid}}{4(C_6H_6O_6)} + 12CO_2 \qquad (2)$$

followed by the decomposition of lactic acid into butyric acid, CO_2, and hydrogen according to (Personne, 1853):

$$\underset{\text{lactic acid}}{4(C_6H_6O_6)} = \underset{\text{butyric acid}}{2(C_8H_8O_4)} + 8CO_2 + H_8 \qquad (3)$$

Red or amorphous phosphorus

Personne wrote that Anton Schrötter (1802-1875) had discussed in detail the chemical properties of red phosphorus (Schrötter, 1848), and Friedrich Wöhler (1800-1882) and Frerichs had referred to its toxic action (Frerichs & Wöhler, 1848). He was now intent in adding some additional properties of this material and challenging the conclusions of Frerichs and Wöhler (Personne, 1857).

According to Schrötter, it was accepted that red phosphorus suffered no modification in contact with atmospheric air, and that it did not combine with oxygen until a temperature of around 260 °C, when it transformed into ordinary or normal phosphorus. According to Personne, this claim was true only if the observation was made on red phosphorus in sufficiently large fragments. Red phosphorus powdered or in small flakes, at atmospheric temperature, absorbed oxygen from the air, without being luminous in the dark, and giving rise to an acidic liquid containing phosphorous and phosphoric acids. The presence of water greatly facilitated this oxidation. Personne put wet powdered red phosphorus on a filter and everyday sprinkled it with a little distilled water; all these washings originated new quantities of acid liquor giving, with silver nitrate, a precipitate which quickly turned black. Fragmented amorphous phosphorus behaved similarly in contact with moist air, although at a slower rate because of its cohesion.

There was always the possibility that the oxidation instead of being due to red phosphorus, came from the slow transformation of red phosphorus into normal phosphorus, which would oxidize as it regenerated. To answer this question, Personne first purified his red phosphorus by multiple washes with water, followed by more washings with boiling carbon disulfide. Afterwards, he put a small amount of the cleaned red phosphorus in several closed tubes and left them in a greenhouse at a temperature of 25° to 30 °C for two months. No phosphorence was observed when these tubes were opened in the dark. Washing the samples with carbon disulfide did not show the presence of normal phosphorus. However, this phosphorus, exposed to humid air, quickly acidified; proving that red phosphorus actually absorbed oxygen from the air (Personne, 1858).

Schrötter also claimed that red phosphorus combined with chlorine at room temperature releasing heat without production of light and generating first phosphorus trichloride and then phosphorus pentachloride. Personne observed something different: contacting chlorine with flakes of red phosphorus located in a small tubular retort, resulted in the ignition of the phosphorus, production of light and phosphorus pentachloride alone. Additional experiments led Personne to conclude that all chemical agents attacked red or amorphous phosphorus in the same manner as did with ordinary phosphorus. although less intensively (Personne, 1858).

Frerichs and Wöhler had reported that phosphorous acid was eminently toxic: 0.5 g of this acid ingested in the stomach of a medium-size dog killed it within an hour. The toxic action was caused by the oxidation of the phosphorus to phosphorous acid in the digestive channel (Frerichs & Wöhler, 1848). Antoine Bussy (1794-1882) and Mathieu Orfila (1787-1853) and Rigout had contested this claim and shown that amorphous phosphorus was harmless to the animal economy (Orfila & Rigout, 1856). Personne also carried some experiments on the subject (Personne, 1857). He fed six dogs amounts of phosphorous acid varying from 0.6 to 1.45 g of anhydrous acid. In all of these animals, the esophagus was bound after the injection of the acid extended into the stomach. To his surprise, the animals all lived six, eight and even nine days after the injection of the alleged toxicant. From his results, he concluded that it was difficult, if not impossible, to attribute a real toxic action to phosphorous acid. The death of the six animals tested, occurring after such a long time, was sufficiently explained by the duration of the abstinence added to the consequences of the operation necessary for the ligation of the esophagus. Personne believed that the results of Frerichs and Wöhler were due to their using an impure sample of phosphorous acid (Personne, 1857).

Personne concluded as follows: (1) red or amorphous phosphorus, without being luminous in the dark, oxidized at ordinary temperature in contact with air, producing the same acids as normal phosphorus; (2) phosphorous acid did not seem to possess the toxic properties attributed to it by Wöhler and Frerichs, and that, consequently, red phosphorus did not owe its harmlessness, perfectly observed on the animal economy, to the absence of phosphorous acid; and (3) phosphorus only produced an adverse effect on the economy when it entered the circulation by absorption. This absorption could only occur with the help of fatty substances, which it met in the digestive tract and in which it dissolved, all the more easily, since it had been ingested in a greater state of division (Personne, 1857).

Turpentine

Personne wrote that Conrad Bromeis (1820-1862) (Bromeis, 1841), S. M. Rabourdin (Rabourdin, 1844), and Amédee Caillot (1805-1868) (Caillot, 1846), had obtained several acids (i.e., terebic, hpyroterebilic, terepthalic, terebenzic, and terechysic) by the oxidation of turpentine with nitric acid in varying degrees of concentration. This was a very violent reaction, which did not allow determining the possible pathway of the reaction. For this reason, Personne decided to carry it using reagents such of KOH or a mixture of KOH or NaOH with CaO (potash or soda lime), which would allow the production of an acid closer to the mother material (Personne, 1856). This turned out to be a very simple process: He passed a stream of vaporized turpentine hydrate, $C_{20}H_{16}$,4HO, over soda lime heated to 400 °C, treated the product with HCl, and isolated an acid, which he named turpentilic acid. The production of this acid by the action of soda lime on turpentine hydrate was accompanied by a fairly abundant evolution of gas composed of methane, and hydrogen, which Personne represented as follows (sic):

$$C_{20}H_{20}O_4 = C_{16}H_{10}O_4 + 4CH2 + H_2 \qquad (4)$$

According to Personne, turpentilic acid was a white solid, smelling faintly like goat, heavier than water, melting at 90 °C, and distilling at 250 °C. Analysis of its calcium and silver salt indicated that its formula was $C_{16}H_{10}O_4$, differing from turpentine by $2C_2H_2 + H_2$. The calcium salt was white and crystallized in small needles; the silver salt was sparingly soluble in boiling water, and the lead one, was non crystallizable and looked like pieces of

Arabic gum. Its ethyl ester was similar to the odorous esters produced by volatile fatty acids and smelled like a mixture of pear and apple (Personne, 1856).

Turpentine as antidote of phosphorus

Personne wrote that nowadays phosphorus had replaced arsenic as the means for suicides, and criminal or accidental homicides (Personne). This substitution had come as a result of the wide use of chemical matches and phosphorus paste for destroying obnoxious animals. It was most dangerous because medicine had no antidote for combating it action: victims would eventually die. According to Jean-Baptiste-Alphonse Chevallier (1793-1879) and Abel Poirier, the uncontrolled sale of red phosphorus was a menace to society; an ease source of the chemical was chemical matches prepared using this element. The matches were treated with water and the solution used for criminal purposes. The poisoning effect was substantially stronger than that of arsenic; antidotes were readily available for poisoning caused by arsenic, copper, zinc, and lead, but none was known for phosphorus. In a booklet published in the subject (Chevallier & Poitier, 1858), Chevallier and Poirier gave a detailed historical review of the large number of cases of phosphorus poisoning (criminal, suicide, or accidental) that had occurred in France between 1824 and 1858, as well as a report of the death of different animals caused by ingestion of pills or solutions containing phosphorus. An important factor were the people working in factories manufacturing this kind of matches, they faced the possibility of becoming affected by jawbone necrosis, a fatal disease accompanied by intense pains. In another publication, Chevallier gave a more detailed explanation of the dangers caused by phosphorus to the health of the workers working in its industry, and as source of many of the fires occurring in France (Chevallier, 1861).

Personne believed that in the present state of the problem, it was highly desired to find an efficient antidote that the physician could use with confidence. He was led to study the possibility of using turpentine as an antidote after hearing of a medical case in which, Pierre Pémartin, an unemployed worker, had attempted suicide by ingesting a paste of phosphorus matches as poison and also drinking 15 g of turpentine dissolved in half a liter of water, believing it would accelerate his death and make it certain (Andant, 1868). Surprisingly, the suicide failed. In addition, it was long known that the essence of turpentine, as well as other hydrocarbons, caused phosphorus to lose the property of being luminous in the dark, and, also, that in an English chemical match factory at Straffort, workers were protected from necrosis of the jaws by making them wear, attached to the chest, a small open vase containing turpentine, the fumes of which were easily within reach of the mouth and nasal passages (Personne, 1869a).

Personne carried on 15 experiments in sets of three, using dogs of medium size and chosen, as much as possible, of the same strength, and kept without food since the night before. All the animals were fed phosphorus under a different set of conditions: the first dog of each series was fed phosphorus alone, the second, was administered turpentine one to two hours after ingestion of the poison, and the third, received the antidote immediately after the phosphorus. In every case the phosphorus was administered as a paste or as a solution in almond oil emulsified with egg yolk, using an esophageal tube introduced into the stomach through the mouth opening. In this form. the toxic material was in the most favorable conditions for absorption and, consequently, for poisoning. The turpentine was administered in the same manner, at a dose of 10 g emulsified with egg yolk. Two of the dogs fed only phosphorus died; most of the dogs which received turpentine immediately, or one or two hours after phosphorus, survived, although they were very sick for some time (Personne, 1869a).

The question was now, how did turpentine neutralize the toxic action of phosphorus? For Personne, the mechanism was not in the manner of ordinary antidotes, which generally had the effect of forming insoluble or inactive combinations with the poison. This assumption was supported by the fact that in every case the turpentine ingested was eliminated without causing major health disorders. The answer to the question required knowing the poisoning track of phosphorus, information unavailable at that time. Personne assumed that phosphorus killed by hindering blood hemoglobin and depriving it of oxygen, death being fast when the absorption by blood was rapid and slow if it was slow. In the first case, death was actually by asphyxia, in the second it resulted from hemoglobin failure. It seemed that the absorbed turpentine hindered the action of phosphorus in blood in the same way that it hindered its combustion in air at low temperature (Personne, 1869a).

In a following publication, Personne used a very original procedure to try to prove that the absorbed turpentine prevented phosphorus from burning in the blood, in the same way as it prevented its combustion at low temperature in the air. Thus, it could be eliminated without having caused disturbances in the economy. The accidents caused by the ingestion of phosphorus were because this body, absorbed and drawn into the circulation, violently seized the oxygen from the blood, and that it was this violent deoxidation of the blood cells, which produced the accidents, most often fatal, which occurred following ingestion of this toxicant (Personne, 1869b).

For his purpose, Personne selected pyrogallol, a compound substantially different from phosphorus, which put in contact with alkalis, absorbed oxygen so fast that it was used by chemists in gas analysis. He administered pyrogallol to two dogs, at a dose of 2 and 4 g, in highly diluted solution, using an esophageal probe inserted into the stomach. Fifteen minutes after the injection, the action was already felt, all the symptoms of asphyxia appeared. taking on all the characteristics of those caused by phosphorus: brown foamy vomiting, deep sadness, trembling, belly retracted, etc. At the end of an hour, the animal moved with difficulty, complained strongly, vomited, emitted brown urine, and exhibited numbness. Eventually, death arrived at the end of 50 hours for the animal fed 4 g, and about 60 hours for the one who had taken only 2 g of the poison (Personne, 1869b).

The autopsy revealed a very large liver and a flabby heart with its cavities containing a very large number of clots of black blood. The bladder was full of a brown liquid resembling the liquor obtained when an alkaline solution of pyrogallic acid was stirred in contact with air. Microscopic examination of the heart and the liver showed the presence of an enormous quantity of fat. These results demonstrated that phosphorus and pyrogallic acid, so different one from the other, showed the same chemical function, that of rapidly absorbing oxygen from the air. To Personne, these results confirmed his assumption that phosphorus killed by asphyxiation, slow or fast, according to the quantity which was absorbed more or less quickly (Personne, 1869b).

Roasted coffee

Personne wrote that the transformations experimented by the principles contained in the green beans of coffee had been little investigated. It was only known that the brown bitter substance and the aromatic principle (caffeone) were the result of the decomposition of the portion of the grain soluble in water, and that a large part of the caffeine disappeared during the roasting, entrained with the volatile products. Green coffee, exhausted by water, then roasted, did not yield to water a bitter substance or an aromatic product (Personne, 1868, 1870a).

Personne collected the volatile products and found that their content of caffeine was so small that its weight could not be evaluated, a result that did not explain the considerable loss which took place during roasting, carried out even under the best conditions. Experimental evidence indicated that this loss was almost half of its weight; green coffee containing 1.45% caffeine, only provided 0.65% for after roasting.

Personne succeeded in showing that the disappeared caffeine seemed to have decomposed into methylamine (a base discovered by Würtz), a small amount of which was found in the condensed volatiles; but most of it remained in the roasted coffee from where it was easily removed with a fixed alkali. The obvious question was to determine if methylamine really originated from caffeine and by what mechanism. To do so, Personne heated caffeine and passed the vapors through a tube filled with pumice stoned heated to 300 °C; the results indicated that very little decomposition had taken place under these conditions. the small amount which decomposed gave, as a characteristic product, only cyanogen. The nature of this decomposition was, moreover, easy to predict; the composition of caffeine, $C_{16}H_{10}N_4O4$ clearly demonstrated that nitrogen could not meet there the quantity of hydrogen necessary for its transformation into methylamine, C_2H_5N. This result proved that caffeine was not the origin of the alkaloid present in the coffee grain. Personne reasoned that for caffeine to give rise to this base it had to be placed under conditions such that it encountered nascent hydrogen. The analysis of coffee, made by Anselme Payen (1795-1871) had shown that most of its caffeine was combined with the tannin of the coffee, forming a double salt with the potassium, which Payen isolated and studied under the name of chloroginate of potassium and caffeine (Payen, 1846; Personne, 1868, 1870a).

Personne tested his hypothesis by preparing caffeine tannate by the reaction been caffeine and nutgall, a substance known to contain a large amount of tannin. This tannate was placed in a small retort provided with a collector and heated to 250°-300 °C. The products were found to be unaltered caffeine in the form of small needles, and methylamine present in small quantities in the condensed products, and especially in the residue of the retort. Among the volatile products, there was a body offering a certain odor analogy with that of roasted coffee, but far from being as pleasant. These results confirmed the assumption that the tannin of coffee provided the hydrogen necessary for splitting caffeine into methylamine (Personne, 1868, 1870a).

Personne added that methylamine could be easily prepared by distilling a cold aqueous extract of roasted coffee with lime or magnesia, but not with strong alkalis such as KOH and NaOH. The resulting alkaline liquor was neutralized with HCl and evaporated to dryness. Treatment of the dry residue with absolute alcohol separated the methylamine salt in a high degree of purity. This salt was treated with a piece of KOH, followed by treatment with water and acetic acid, yielding methylamine acetate. This product was identified by its physical and chemical properties and by the double chloride it formed with platinum (Personne, 1868, 1870a).

The question arose about whether methylamine acetate was the principle, or one of them, giving place to the stimulating power of coffee. Louis-Jules Béhier (1813-1876), a physician at Hôpital La Pitié, examined this substance and reported that it increased the arterial pressure but did not affect the pulse except in high doses (Personne, 1870a).

Personne remarked that hot caffeine was easily dissolved by carbon disulfide and benzene. The dissolving power of benzene, in particular, was such that this vehicle could be usefully employed to obtain caffeine in a high state of purity (Personne, 1868).

Quinine in urine

Personne wrote that most scientists had accepted the notion that the quinine eliminated by the urine did not undergo any modifications by its passage through the economy. Nevertheless, G. Kerner reported the synthesis of an oxidation product of quinine, which he called dihydroxylquinine, a product devoid of the flavor bitter characteristic of quinine, while retaining the other properties of this alkaloid, among others of being precipitated by tannin, etc., as well as the fluorescence of its sulfate (Kerner, 1869). Kerner admitted that this dihydroxylquinine was produced in the economy and that it was in this form that the ingested quinine was excreted in the urine. Afterwards, Guyochin, in his doctoral thesis that he defended in 1873, at the Faculty of Medicine of Paris, claimed that the quinine eliminated by the urine was not an oxidation product of this base, but simply an isomeric modification, quinidine (Personne, 1878).

Personne carried experiments on the subject and concluded that the different results obtained by Kerner and Guyochin were simply due to the extraction procedures they had employed particularly by Guyochin. His extraction method had the following disadvantages: (1) ether was unable to dissolve the quinine combined in the acid combinations, which existed in simply evaporated urine; and (2) quinine, subjected for a very long time to the action of the heat necessary for the evaporation of a large mass of liquid, was most certainly transformed into quinidine (Personne, 1878).

After much testing, Personne developed the following separation process, which he believed was free of the shortcomings of those employed by Kerner and Guyachon. In it, the quinine was precipitated directly in the urine using a tannin solution. The tannate was washed on a filter and mixed with powdered calcium hydroxide. The dried and powdered mass was extracted with pure, dry chloroform, and the filtered solution evaporated to dryness. The residue was a mixture of the alkaloid with a resinous matter, easily separable with diluted sulfuric acid. The resulting material was transformed into quinine basic and acid sulfate and their composition verified by standard testing (Personne, 1878).

According to Personne, his results clearly proved that the quinine eliminated by the urine had not undergone any alteration or molecular modification. Personne also inquired about the destiny of the part of the quinine that had been ingested by the animal economy. He reported that he had always obtained, at the same time as the quinine, a certain quantity of resinous matter, in everything like that which one obtained in the analysis of good quinquinas. In his opinion, this resinous matter arose from the destruction of quinine, of which it was only the residue, and concluded as follows: (1) the quinine eliminated by the urine had undergone no alteration by its passage through the economy; and (2) a large amount of the quinine *ingested* was completely destroyed within the economy (Personne, 1878).

Chloral

Personne prepared chloral by using the procedure of Jean-Baptiste André Dumas (1800-1884), its discoverer (Dumas, 1834). Basically, it consisted in bubbling dry chlorine through absolute alcohol, taking the proper safety measures. The chlorine was prepared by treating a mixture of sodium chloride and sulfuric acid with manganese dioxide. The resulting liquor was mixed with two or three times its volume of concentrated sulfuric acid, followed by distillation under controlled conditions; the passing liquid was distilled again at 94^0-95 °C and the process repeated once, and then again, in the presence of a diluted solution of calcium hydroxide. The resulting anhydrous chloral was mixed with one time its volume in water and the resulting solution evaporated to dryness to obtain the chloral hydrate in a crystalline state. The many preparations performed by Personne allowed him to improve substantially the original Dumas' procedure: (1) he found that it was not necessary to use absolute alcohol, it was enough to utilize the available commercial alcohol of 95° and increase its concentration to 97° by distilling it in the presence of dry potassium carbonate, with the corresponding economical advantage; (2) at the beginning of the operation it was advantageous to cool the alcohol because the initial reaction was exothermic and the increase in temperature resulted in the loss of part of the alcohol; (3) to increase the yield, it was convenient to assure that all the alcohol was attacked simultaneously. This objective was achieved when the alcohol kept a yellow color during all the reaction, despite the temperature increase; (3) the gross product of the reaction should be washed several times with sulfuric acid free of nitrous vapors; and (4) the first distillation should be done in the presence of the calcium hydroxide to assure the elimination of the HCl formed (Personne, 1869, 1870, 1874).

The dry chloral was converted into its hydrate by mixing it with two equivalents of water (about 12.3% of the weight), a very exothermic process that could raise the temperature to about 100 °C. The accompanying boiling could result in part of the hot mass being thrown out of the vessel, with the corresponding danger of burns and loss of product (Personne, 1869, 1870, 1874).

Personne wrote that anhydrous chloral was a colorless liquid of fatty touch, tasting acrid and caustic, and a penetrating odor that violently excited the nostrils and provoked lacrimation. It boiled at 96 °C without decomposition and had specific gravity 1.502 at 18 °C. Heated, it easily dissolved phosphorus, sulfur, bromine, chlorine, and iodine. It was very avid of water forming the hydrate $C_4HCl_3O_2$, H_2Cl_2. It dissolved and combined with alcohol. By its origin, it should be considered an aldehyde, showing the main properties of this function. It combined with ammonia gas, producing white fumes. In the dry state, it was not attacked by sulfuric acid even at 100 °C. It was attacked by nitric acid yielding first trichloroacetic acid and eventually chloropicrin (Personne, 1869, 1870, 1874).

Chloral hydrate was a solid mass formed by tangled crystals, having a strong and penetrating odor, fatty to the taste, deliquescent and becoming a syrupy liquid, acrid and burning taste, and giving a slightly acid reaction with litmus paper. The crystals melt at 46 °C and boiled at 97 °C. It was destroyed by concentrated sulfuric acid and transformed by nitric acid into trichloroacetic acid. Alkaline hydroxides transformed it into chloroform and alkaline formiate (Personne, 1869, 1870, 1874).

Personne studied the reaction between chloral and alcohols and described the properties of the corresponding chloral alcoholates (methylate, ethylate, isopropylate, and amylate). He also studied the reaction of chloral and albuminoidal substances, such albumen, blood, muscle flesh, fibrin, and brain matter (Personne, 1869, 1870, 1874).

In 1869 Oscar Liebreich (1839-1908) published a paper reporting that chloral hydrate, $C_4HCl_3O_2$, H_2O_2, decomposed in the presence of alkalis, NaOH and alkaline carbonates, into chloroform and sodium formate, according to the equation (Liebreich, 1869):

$$C_4HCl_2O_2,H_2O_2 + NaO,HO = C_2HCl_3 + C_2HNaO_4 + HO \qquad (5)$$

Liebreich believed that this transformation should also take place inside the animal economy, thanks to the alkalis it contained, with the chloroform generated producing the pertinent anesthesia effects. Some French physicians accepted this assumption while others rejected it claiming that the chloral hydrate produced this effect by itself and not by its decomposition (Personne, 1869c, 1870, 1870,1874).

Personne believed that the divergence of opinions was due to the use of chloral hydrate not sufficiently pure. Hence, he decided to carry his own experiences use a highly pure chloral hydrate, prepared by himself.

Personne mixed beef blood with a small amount of chloral hydrate and noticed that no coagulation took place, and the absence of chloroform smell even when the mixture was heated to 40 °C; the only odor was that of blood. Feeding a dog by the mouth 3 g of the hydrate showed effects after about 10 minutes; addition of another 3 g resulted in complete anesthesia. No chloroform smell was felt in the air exhaled by the animal during the complete experiment. The animal was killed, and its jugular blood found not to exhibit the odor of chloroform, only that of blood. These results seemed to support the opinion of the physicians that did not believe that the hydrate was split during its passage through the economy. Anyhow, Personne, decided to test the behavior of the hydrate with an alkaline animal liquid like blood, but absent of odor. For this purpose, he selected the white of eggs dissolved in a little of water, heated to 40 °C in a water bath. This time he clearly perceived the smell of chloroform. This result suggested him that the same phenomenon occurred with blood, except that its odor *masked* that of chloroform. Hence, he decided to see if he could isolate the possible chloroform generated. For this purpose, he repeated the experiment with beef blood, this time putting the ingredients in a distillation vase, heated to 100 °C in a water bath, and capable of condensing the volatile products. The passing fraction condensed as a two-layer liquid, of which the lower one was found to be a small amount of chloroform. He understood that this result was obtained with blood at a temperature well about that of the body, hence he repeated at 40 °C; this time the possible amount of chloroform produced was too small to give a definite answer. To avoid this problem, he decided to use the toxicological test for chloroform, based on destroying by heat the chloroform into chlorine and HCl, which could be detected with silver nitrate. This procedure produced a large amount of silver chloride. The same result was obtained with the blood of the dog, except that the amount of silver chloride obtained was somewhat smaller, and also with the stomach liquid obtained from the dead dog. These results proved clearly that Liebreich was correct in assuming that chloroform was generated inside the body and was able to produce anesthesia (Personne, 1869c, 1870, 1870,1874). Afterwards, Personne proved that all the strong and weak alkalis, magnesia, alkaline salts like sodium and potassium bicarbonates, sodium borate and phosphate, and all the alkaline animal liquids such as blood and the white of egg, were able to transform chloral into chloroform a 40 °C (Personne, 1874).

Personne explained this result based on previous experiments that had shown that chloral hydrate combined with albuminoidal matter and with the cerebral and nervous matter (Personne, 1874). These compounds were attacked by the blood alkalis and transformed into chloroform and alkaline formiates., although rather slowly. Personne added that he had never found chloral or chloroform in the urine of patients treated with chloral hydrate, no matter what the size of the dose. It was known that this urine reduced the Fehling liquor, but this was due to the alkaline formiate known to be present in this kind of urine. The final destruction of chloral gave two molecules of formic acid, together with the chloroform. The latter was destroyed by a following action into formic acid and alkaline chloride, as shown by the following reactions:

$$C_4HCl_3O_2 + NaOHO = C_2HCl_3 + C_2HNaO_4 \tag{6}$$

chloral chloroform sodium formiate

$$C_2HCl_3 + 4NaO,OH = C_2HNaO_4 + 3NaCl + 4HO \tag{7}$$

chloroform sodium formiate water

This final transformation of the chlorate into sodium formiate and sodium chloride, both eliminated by the urine, explained the increase of these chlorides in this liquid, as well as their reducing power of the Fehling liquor (Personne, 1869c, 1870, 1870,1874).

In another publication, Personne addressed the question of the difference in the physiological action that existed between chloral and chloroform (the action of chloral lasted longer than that of chloroform) (Personne, 1874). For this he considered the fact that the splitting of chloral produced formic acid. This acid, burnt by the animal economy, produced CO_2 whose hypnotic action enlarged that of chloroform. As shown by equation (6), 100 parts of chloral gave place to 72.20 of chloroform and 27.80 of formic acid. An important part of this chloroform was destroyed yielding formic acid and sodium chloride (equation 7). All this formic acid was burnt, and partially eliminated by the urine because the latter was able to reduce the Fehling liquor, even when deprived of glucose. A material balance indicated that the total decomposition of 100 g of chloral hydrate produced 56 g of formic acid. Hence, a dog normally fed 10 g of chloral hydrate, took 5.6 g of this acid (Personne, 1874).

According to Personne, his experience indicated that fresh blood mixed with chloral hydrate, and kept at ordinary temperature, coagulated completely, keeping its red color. Albumin also combined with chloral; the resulting combination was soluble in excess of albumen or of chloral. It was accepted that albuminoidal matter was an amide, and that these compounds were able to combine with aldehydes. Hence, it was reasonable to admit that chloral, known to be a trichloroaldehyde, was able to combine with albumens. This combination explained the longer action of chloral relative to that of chloroform. The first action of chloral hydrate on albuminoidal matter produced chloroform, at the expense of their alkali. The impoverished residue combined with the chloral not destroyed turning into a kind of reservoir of chloroform, that was not released immediately, only the circulation destroyed it. This assumption explained why little chloral was found in the blood of animals under the influence of chloral (Personne, 1874).

All the above work led to the doctoral thesis of Personne (Personne, 1877).

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