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ADRIEN ARMAND MAURICE HANRIOT

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Abstract: Adrien Armand Maurice Hanriot (1854-1933) was a French physician and chemist who studied in detail the preparation of glycerin derivatives, the substitution of hydrogen in hydrocarbons by alkali metals, physiological phenomena in human beings, in particular, the exchange phenomena in the respiratory system, the derivatives of strychnine, etc. Among his many discoveries we can mention the lipase in blood, chloralose and parachlorose.

Keywords: chloralose, strychnine, physiology, glycerin, vegetable principles, breathing.

Resumen: Adrien Armand Maurice Hanriot (1854-1933), médico y químico francés que estudió en detalle la preparación de derivados de la glicerina, la sustitución del hidrógeno en hidrocarburos por álcalis, fenómenos fisiológicos en el hombre, particularmente los intercambios en el sistema respiratorio, los derivados de la estricnina, etc. Entre sus muchos descubrimientos se pueden mencionar la lipasa en la sangre, la clorosa y la paraclorosa.

Palabras clave: cloralosa, estricnina, fisiología, glicerina, principios vegetales, respiración .

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LIFE AND CAREER

Maurice Hanriot, born in Confians-Sainte Honorine (Seine-et-Oise) on March 24, 1854, was the son of Armand Eugène Remy Hanriot, notary and mayor of Confians, and Camille Félicité de Sens There seems to be no information about Hanriot's early life and education; most of it is available in his dossier at the archives of the Legion d'Honneur.[1] Hanriot received his basic education at the Collège Rollin, in 1873 he received his degree in physics (licencié ès sciences physiques), and six years later his doctorate in physics (docteur ès sciences physiques) from the Faculty of Sciences in Paris and his doctorate in medicine from the Faculty of Medicine in Paris, after successfully defending theses on derivatives of glycerin[2] and muscular electricity.[3] The latter won him a silver medal from the Faculty of Medicine (1879). During his doctoral studies he worked as physics assistant (préparateur de physique) in the laboratory of Paul Quentin Desains (1817-1885) at the Faculté des Sciences (1873-1879) and chemistry assistant (préparateur de chimie) at the Faculty of Medicine (1875), replacing Joseph Aquiles Lebel (1847-1930). After graduation he followed a successful academic career at the Faculty of Medicine: agrégé (1880), after presenting a thesis about the constitution of matter;[4] in charge of the course auxiliaire de chimie (1880-1884); substitute of Charles-Adolph Würtz (1817-1884) (1881-1883); head of chemical works (1884-1895); and professor at the École Municipal

de Physique et Chimie (1888). In addition he occupied several public and professional positions: head of essays at the Administration des Monnaies et Médailles (French Mint); member of the Académie de Médicine (1894), officer of the Académie de Médicine (1889) and treasurer of the same (1896); member of the Conseil d'Hygiène et de Salubrité Publique (1897) and of the Commission d'Hygiène Industrielle (1901); general secretary and then President, of the Société de Chimique de Paris (1886-1893); secretary of the organizing committee of the 1889 Chemistry Congress held in Paris; member of the organizing committee of the 1893 Chemistry Congress, held in Chicago, member of international commission of chemistry nomenclature; and honorary member of the Société de Physique et d'Histoire Naturelle de Genève. The Académie des Sciences awarded him half of the 1890 Jecker prize for his work in pure chemistry and the Académie de Médicine awarded him the 1893 Buignet prize for his work on the assimilation of glucose by a healthy and a diabetic person.

Hanriot was appointed chevalier of the Légion d'Honneur in 1899, promoted to officier in 1908, and to commandeur in 1921. Hanriot was married to Marie Duclos; their two sons, Robert and Armand, were educated as physician, He passed away on August 31, 1933, in La Lisses (Seine-et-Oise).

SCIENTIFIC WORK

Hanriot published over 70 papers and books [5,6,7,8] in the areas of organic and analytical chemistry, biology, and physiology. As customary for all candidates to the Académie de Médicine and the Conseil d'Hygiène et de Salubrité Publique, Hanriot published booklets describing his academic activities and his research and results. [9,10] In addition to the subjects discussed below Hanriot studied glycerin and its derivatives; [11,12,13,14,15] hydrogen peroxide; [16,17] natural principles in plants; [18,19,20] the synthesis of stilbene; [21] isoxasol and derivatives [22,23,24,25] the polymerization of ethyl cyanide; [26] the action of potassium on phenyl derivatives; [27,28,29] etc.

Strychnine

In 1881 Adolph Claus (1838-1900) and R. Glassner reported that they had obtained dinitrostrychnine nitrate by passing dinitric trioxide (N_2O_3) into an alcoholic solution of strychnine or by boiling strychnine nitrate with concentrated nitric acid. Dinitrostrychnine, $C_{22}H_{20}(NO_2)_2N_2O_2$, was prepared by adding ammonia to the nitrate; this compound crystallized from alcohol in red orange leaflets, which darkened on exposure to the air; it melted at 226 ℃ and was insoluble in common solvents except alcohol. [30] Hanriot found that the reaction of strychnine with fuming nitric acid produced a dinitrostrychnine different from that of Claus and Glassner. [31] He obtained this derivative by

dissolving strychnine in fuming nitric acid kept at -10 ℃ and taking care that the temperature did not exceed -5 ℃. Addition of a large amount of water to the product of the reaction resulted in the crystallization of dinitrostrychnine nitrate, which was separated, redissolved in water, and reprecipitated by addition of ammonia. According to Hanriot, dinitrostrychnine, $C_{22}H_{20}(NO_2)_2N_2O_2$, crystallized as long yellow amber transparent prisms; it was soluble in alcohol and boiling water, little soluble in cold water and very soluble in chloroform. It did not melt but decomposed at about 220 ℃. Its salts were little soluble in water and soluble in concentrated acids; dinitrostrychnine nitrate crystallized as leaves and the chlorhydrate as a cheesy mass. The chlorhydrate was reduced by the sodium amalgam yielding a strongly colored liquid; treated with tin and HCl yielded the chlorhydrate of a new base, diamidostrychnine, $C_{22}H_{20}N_2O_2(NH_2)_2$, which crystallized as prisms that did not melt and began to decompose at about 225 ℃. It was little soluble in water and in ether and soluble in alcohol and chloroform. Treated with sodium hypochlorite it produced a green precipitate; treatment with sulfuric acid and potassium dichromate did not generate the violet color typical of strychnine, and boiled with ferric chloride produced a red solution. [31]

In 1883 Hanriot and Charles Blarez (1852-1918) reported the results of their experiments on the solubility of strychnine in different inorganic and organic acids. [32] Strychnine was found to be sparingly soluble in acids, the solubility increased as the acid became more diluted. In practice, the phenomenon was more complicated: Treating a concentrated solution of a neutral salt of strychnine with a slight excess of a variety of acids (sulfuric, HCl, nitric, oxalic, tartaric, and acetic), resulted in the formation of the pertinent salt accompanied by a small amount of the corresponding acid. The precipitate formed with difficulty when the salt solution was highly diluted; curiously, agitation increased the rate of formation and the precipitate was less abundant when using the same acid as the anion of the salt. The precipitate redissolved in an excess of acid and precipitated again when enough water was added to make the solution very diluted. [32]

Hanriot and Blarez described in details the synthesis of strychnine sulfate and hydrochloride. Addition of a small amount of sulfuric acid to a saturated solution of strychnine sulfate converted the liquid into a mass of fine needles composed of strychnine sulfate, $C_{22}H_{20}(N_2O_2)_2H_2SO_4$, accompanied by less than 1.13/1000 strychnine. The same result was obtained when adding a small amount of HCl to a saturated solution of strychnine hydrochloride. Strychnine sulfate was found to be very soluble in water; addition of HCl precipitated the salt as its neutral chlorhydrate. Hanriot and Blarez added that diamidostrychnine behaved in a similar manner and that the oxidation of strychnine with potassium permanganate, followed by treatment with cupric sulfate, yielded the copper salt of a nitrogenated acid, non crystallizable. [32] Hanriot studied this copper salt in detail. He dissolved it with a diluted solution of ammonia and evaporated the resulting liquid to dryness. The resulting

ammonium salt, treated with soluble salts of lead, silver, or copper, yielded precipitates from which the acid was easily recovered; 25 g of original strychnine yielded about 12 g of the acid; its elemental analysis corresponded to the formula $C_{11}H_{11}NO_3$, H_2O. This hydrate lost its water at about 100 ℃. It was insoluble in water and ether and soluble in alcohol and alkaline or acid solutions. [31]

In 1875 Franz Leopold Sonnenschein (1819-1879) reported that the reaction of brucine with diluted nitric acid produced CO_2, a yellow resin, and strychnine. [33] Hanriot repeated Sonnenshein's reaction using pure brucine and was unable to detect the presence of strychnine in the resulting product. He believed that the discrepancy in results indicated that Sonnenschein had used brucine contaminated with strychnine. Consequently, he carried the reaction using a mixture of 2 parts of brucine and 1 of strychnine and found that the resulting product contained the same amount of strychnine as the raw material. [34]

Hanriot published an additional paper summarizing all his findings about strychnine and properties. [35]

Physiology

Hanriot, alone, or with Charles Richet (1850-1935; 1913 Nobel Prize in Physiology or Medicine), published a large number of papers regarding human respiration. [36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54]

Dosage of oxygen

Hanriot and Richet developed a new and simple apparatus for determining the consumption and production of the respiratory gases, which did not require weighting or the direct dosage of these gases. The basic element of their apparatus was a set of three consecutive gas meters, the first one (#1) measured the volume of air inspired, the second (#2) the volume of air expired, and the third (#3) was a general-purpose meter. When a solution of KOH was interpolated between meters #2 and #3, the difference of their readings represented exactly the amount of CO_2 absorbed while the difference between the readings of meters #1 and #3 indicated the amount of oxygen absorbed. The apparatus for retaining the CO_2 consisted of a 1.5 m long test tube filled with pumice stone or glass particles, wetted constantly by a well-dispersed stream of concentrated KOH. Careful calibration of the high-precision gas meters allowed reducing the potential error to less than 50 cm^3 for a total volume of several cubic meters of gas. [36], [37]

An additional paper described a graphical procedure for inscribing the absorption of CO2 in the KOH solution. [42]

Respiration

Hanriot and Richet's first paper on the subject had for purpose determination of the role played by accelerated or retarded ventilation (amount of air circulating by the lungs) on the exhalation of CO_2. [38] All the experiments were carried on, as much as possible, equal physiological conditions. The noses of the participants were blocked with pressure pegs and their mouths by a special mask. These painful conditions forced the length of the experiment to no more than 30 minutes. The results of two series of experiments indicated that at the end of a very short time (10 to 20 minutes) the rhythm of ventilation was slightly different of the normal one. During this period, the absolute amount of CO_2 expired grew continuously until after about 20 minutes it became the same as that of a normal or slow respiration. According to Hanriot and Richet, these results proved clearly that the production and excretion of CO2 were two different functions; the production was independent of the excretion and the latter could be voluntarily modified during several minutes. In addition, when the lung ventilation was increased at will, more CO_2 was excreted, but sooner or later, the rate became normal again. [38]

It was well known that muscular work was the most significant factor that affected the respiratory exchanges. In order to quantify this phenomenon Hanriot and Richet carried a series of experiments to determine the relative variation of the air volumes circulating in the lungs and of their centesimal composition. [39] The test subject was a male 48 years old, weighing 50 kilos and subject to a regular food regime, which was instructed to turn a wheel at different regimes (moderate and strong), resting in between. The ventilation rate, in liters/min, and the oxygen and CO_2 content, were determined every minute during the duration of the experiment (about 5 minutes). The results indicated that the excess ventilation (above the normal rate) was proportional to the muscular work, varying in the same amount for each turn of the wheel, while the content of oxygen and CO_2 remained unchanged for the different volumes of air exhaled. On the one hand, a moderate increase in the intensity of the work done did not require additional ventilation; on the other hand, ventilation was insufficient during strenuous work. The centesimal variations of oxygen absorbed during muscular work differed slightly from those of the CO_2 excreted. During moderate work the ventilation was more than enough for the excretion of the CO_2 produced and the absorption of the required oxygen. [39]

In a following experiment, Hanriot and Richter measured the amounts of chemical and mechanical work that took place when an individual raised an object weighing 18 kg to a height of 0.5 m and then released it. [40] This operation was carried on many times, while simultaneously measuring the accompanying respiratory changes. The chemical work associated with the mechanical one was represented by the difference between the rates of normal breathing and breathing during execution of the work. The average results for 10 cycles (lifting and dropping)

indicated that the excess ventilation, excess CO_2, and excess oxygen, were 10.8, 0.494, and 0.326 L, respectively. In other words, the excess oxygen absorbed was always less than the amount of CO_2 released. Further calculations required consideration of the work done in elevating the arms and all the body movements accompanying any muscular exercise. Subtraction of the corresponding amounts or work reduced the above amounts of CO_2 and oxygen to 0.401 and 0.301 L, respectively. Put in another form, each 100 kgm of mechanical work was accompanied by the absorption of an additional 11 L of air by the lungs, absorption of 0.300 liters of oxygen and release of 0.400 L of CO_2, above the normal rates when at rest. [40] Hanriot and Richet tried to estimate the amount of heat released by these changes. They believed that the CO_2 probably originated from the combustion of glucose, but realized that the amount of glucose contained in the body was insufficient to justify the large quantity of CO_2 released by any muscular contraction. Hence, it was necessary that the organism be constantly producing glucose at the expense of other substances, probably fats, glycerin, and albuminoidal substances. In other words, the chemical reaction explaining the ratio of oxygen consumed to CO_2 released during muscular contraction was more complicated than the simple combustion of glucose or glycerin. [40]

Another work related to the physiological effect of carbon dioxide injected through the anus, which was being used as a possible treatment of tuberculosis. [41] The treatment was applied to a lying down 25-year old male patient, weighing 66, and suffering of tuberculosis. Measurements were taken to determine lung ventilation, oxygen absorption, CO2 exhalation, and the ratio O_2/CO_2 in the exhaled air, before and after anal injection of a stream of CO_2. The results indicated that CO_2 injected through the rectum was absorbed almost immediately and reappeared completely in the products of respiration, initially very fast, and then more slowly. An interesting result was that the absorption of oxygen did not follow the same rate of elimination of CO_2, for example, in one experiment the normal amount of oxygen was 12.25 L in half and hour, and 11.35 L in the following half and hour. According to Hanriot and Richet, CO_2 injected in the large intestine passed rapidly into the blood to be eliminated by the lungs, but its presence in the blood caused vigorous respiratory movements and a very active ventilation and respiration. These results had to be taken into account in the development of any theory about respiration. [41]

Hanriot and Richet also studied the effect of the nature of the food ingested on the respiratory exchanges. [43,44] The test subject was a male 48 years old, weighing 50 kilos, and subject to different food regimes (fasting, only meat, fats, glycerin, or starchy matter). Their results indicated that digestion and movement were the two main factors that increased the amount of CO_2 excreted. Of all the feed regimes, only the one based on starchy matter resulted in an increase of the CO_2 produced during digestion. The ratio CO_2/O_2 was 0.72 during fasting and increased to 1.25 during the regime based on starchy food. These results indicated

that the process was not the simple combustion of glucose. The excess of CO_2 found originated from the conversion of glucose into fats, a process that could only take place with release of CO_2, without absorption of oxygen. During muscular work, the excess of CO_2 produced was exactly proportional to the amount of work done, accompanied by an increase in the CO_2/O_2 ratio from 0.72 to 0.90. The body reserves of glucose were too small to admit that the burning of glucose provided the necessary energy. Hanriot and Richet believed that the source of the energy originated from the burning of the glycerin contained in the fatty material. This assumption was justified by the fact that when the diet was strongly based on glycerin, the ratio CO_2/O_2 remained unchanged during rest and work. The results of the different diets indicated (a) nitrogenous foods slightly modified the respiratory exchanges; (b) starchy food increased ventilation and absorption of oxygen, and particularly, the production of CO_2; (c) in a fasting adult male, the hourly ventilation was eight liters per kilo, accompanied by a production of 0.5 g of CO_2 and an absorption of 0.45 g of oxygen. After digestion, these figures changed to nine liters, 0.6 g, and 0.5 g/kg, respectively. [43,44]

Hanriot and Richet also studied the chemical phenomena accompanying respiration when a dog was subject to a strong application of electricity. Richet had already reported that this treatment caused the muscles to behave in a similar manner that under tetanus (for this reason he named it electrical tetanus), although it resulted in a rapid increase in temperature and death by hyperthermia within half-an hour. [45] Their results indicated that as a consequence of the application of electricity (a) the ventilation of the dog increased from 23 L per kilo and per hour in the normal state, to more than double in the electrified state; (b) the amount of CO_2 excreted increased from 1.2 to 4.2 liters per kilo and per hour, while the portion of CO^2 in the expired air increased only from 2.6 to 4.2 %; (c) the ratio CO_2/O_2 changed very little; and (d) the excess of calories produced by the excess of intramuscular combustion accounted for most of the increased in temperature of the animal (50 to 75 %). The remaining amount corresponded to mechanical work and radiation. [45]

In 1891 Hanriot and Richet published a long memoir (60 pages) summarizing all their findings about respiration exchange in humans. [46] The first part was a detailed description of the apparatus employed and the experimental techniques; the second described the experiments conducted on the average of the respiratory exchanges occurring in the test specimen, a 48-year male, weighing about 50 kg. The gross results indicated that the ventilation was 9.900 liters per kilo and per hour, the CO_2 excreted 0.640 5 g, the ratio CO_2/O_2 0.841, the proportion of CO_2 in 100 volumes 3.54 (as volume %), and the proportion of O_2 absorbed in 100 volumes, 4.23 (as volume %). These figures were then corrected according to the feed regime (fasting and normal), and muscular work. Thus, the net amount of CO_2 excreted became 0.500 g for fasting and 0.580 g for normal digestion. The respiratory quotient, CO_2/O_2, was more or less constant for fasting and quite variable according to nature

of the food intake (starchy, nitrogenous, etc.); it hardly changed for a food intake based on fats and nitrogenous ingredients. The ventilation varied along the day (daylight or night), medicine intake, composition of food intake, temperature, rectal injection of CO_2, nervous state (hysteria and hypnotism), etc. The third and fourth section described the influence of the nature of the food intake and muscular work on the different respiratory exchanges. The last part listed the general conclusions, for example: (a) the average ventilation (fasting, digestion, and work) was 10 L of air per kilo and per hour, with 0.65 g of CO_2 produced, a ratio $CO_2/O_2 = 0.84$, and 3.5 for the proportion of CO_2 in the expired air; (b) these figures decreased during a fasting regime to 8.5, 0.50, 0.78, and 3.35, and increased to 9.5, 0.570, 0.84, and 3.30, respectively during a digestion regime; (c) the excess of ventilation due to digestion was 1 liter per kilo and per hour, with an accompanying 0.07 g excess of CO_2; (d) an increase in carbohydrate ingestion resulted in an increase in the respiratory quotient, reaching values above 1 for a diet based exclusively on sugar; (e) fatty and nitrogenous diets caused minor changes in the ratio CO_2/O_2 and the ventilation; (f) for a normal person the minimum ventilation and minimum CO_2 excreted were 6.6 liters and 0.425 g, respectively; (g) the intensity of the respiratory changes varied between daylight and evening, increasing between 8 AM and 5 PM, and decreasing between 5 PM and 8 AM; (h) cold baths and a low temperature increased substantially the ventilation, etc. [46]

Nickel tetracarbonyl

In 1890 Ludwig Mond (1839-1909), Carl Langer (-1935), and Friedrich Quincke (1865-1934) discovered that passing a stream of CO over highly divided nickel at about 50 ℃, resulted in the synthesis of nickel tetracarbonyl, Ni(CO)4, which at 150 ℃ decomposed completely into its components. The carbonyl boiled at 43 °C and 751 mmHg without decomposition, evaporated rapidly at ordinary temperature in a current of other gases, and solidified at -25 °C forming needle-shaped crystals. Both the liquid and the vapor were poisonous, the latter approximating CO in this respect. Experiments with rabbits showed that a sub-cutaneous injection of a very small dose of a solution of the liquid in chloroform led to an extraordinary reduction in temperature, amounting in some cases to 12 °C. [55]

According to Hanriot and Richet one molecule of nickel tetracarbonyl contains, by weight, 65 % of CO so that 1 g of it released 500 cm3 of gaseous CO, an amount able of displacing the oxygen of 2 kg of blood. [47] In a few words, 0.1 g of nickel tetracarbonyl was able to complete intoxicate 200 g of blood. Initial experiments showed that the blood did not decompose immediately this highly toxic compound so that it could be injected in appreciable amounts without causing immediate death. Thus, a rabbit injected 0.1 g of the carbonyl into the venous blood died after several hours. Since the rabbit contained about 160 g of blood, a

dose of 0.08 g of carbonyl should have been enough to kill it, if the decomposition had been immediate. Similar results were obtained with a dog weighing 9 kg; injection of 0.30 g of carbonyl killed it after several hours. Analogous results were obtained when the carbonyl was injected in the eye or in the peritoneum. A spectroscopic analysis of the blood of a poisoned rat showed the typical rays of CO. [47]

Hanriot and Richet commented that in addition to its poisonous effects nickel tetracarbonyl was an extremely dangerous material because it exploded violently and its vapors caused painful headaches. Consequently, it should be used only in well-aerated large rooms. [47]

Chloralose

Hanriot and Richet carried on a detailed study of chloralose (glucochloral, $C_8H_{11}C_{l3}O_6$) a poisonous compound, synthesized the first time by Arthur Heffter (1859-1925) in 1889 from glucose and chloral56 and widely used as a human and veterinary hypnotic agent, to anesthetize laboratory animals, and as rodenticide and avicide. Their work on this compound arose from their search of substances, which slowly released chloral in the organism, such as the chloralides, particular lactic chloralide. [48,49,50,51,52,53,54,55,56,57,58] In their first paper they reported that lactic chloralide proved to be a failure because it had no hypnotic properties and produced serious side effects, such as epileptic attacks with strong bronchial secretions and asphyxia. The results with anhydroglucochloral, a product of the reaction between glucose and chloral, proved to be very satisfactory. [48] They prepared chloralose by heating at 100 ℃ in a flask during one hour, equal amounts of anhydrous chloral and dry glucose. The resulting mass was treated with a little of water and then with boiling ether. The ethereal extract was steam distilled until all the remaining chloral had passed over. The residue was purified by successive crystallizations, yielding a substance a, which was little soluble in cold water, very soluble in hot water and alcohol; and another substance b, sparingly soluble in hot water. The yield of substance a was only 3 %; this product crystallized as fine needles, melting at 184-186 ℃ and volatilizing without decomposition. Elemental analysis gave a composition corresponding to the formula $C_8H_{11}C_{l3}O_6$. Body b crystallized as beautiful pearly scales melting at 229 ℃. Hanriot and Richet suggested naming body a *chloralose* and body b *parachoralose*. They reported that chloralose was a very interesting substance because it had two seemingly contradictory properties: it was hypnotic and at the same time it increased the excitability of the spinal chord. [48]

Dogs could be fed up to 0.6 g of chloralose per kilo, by stomach digestion, and become anesthetized without fatal results. The hypnotic effect began to be felt at 0.2 g/kg, showing that chloralose was more active than chloral. This action was not due to a split of the compound into chloral because the complete decomposition of 0.2 g of chloralose yielded only 0.1 g of chloral. Hanriot and Richet added that a dose of 0.1g/kg

was toxic to birds and cats; they also personally ingested chloralose in amounts increasing from 0.05 g to 0.75 g without toxic effects; doses from 0.30 g and up showed hypnotic effect. Hence, chloralose should not be considered a dangerous substance. [48]

A more detailed study of both isomers indicated that a chloralose melted at 187 ℃ and its aqueous solution did not react with silver nitrate and with Fehling's liquor, even at its boiling point.49 The diluted acids did not split it into its components and alkalis colored brown its aqueous solutions. It reacted with concentrated acids and acid chlorides, yielding di- and tetra-substituted esters; tetracetyl chloralose and tetrabenzyl chloralose melted at 145 ℃ and 138 ℃, respectively. The oxidation of chloralose yielded chloralic acid, $C_7H_9Cl_3O_6$, and CO_2, crystallizing as needles melting at 212 ℃. Parachloralose was insoluble in most reagents, it melted at 227 ℃ and transformed into parachloric acid. According to Hanriot and Richet, both isomers contained the three chlorine atoms of chloral and the aldehyde group of chloral joined with glucose, yielding a compound containing the group C-CC_{l3}. This fact explained why chloralose did not react with hydroxylamine and phenylhydrazine and was not reduced by hydrogen. [49]

The high activity of chloralose allowed injecting it by intravenous or intra-peritoneal via; larger doses could be mixed with milk and ingested orally. Henriot and Richet studied the physiological effects of different amount of chloralose on dogs, cat, chicken, rats, ducks, etc. They found that all the treated animals became insensitive, although their motor power was not abolished, as they did not react to excitations normally painful to untreated specimens. It was clear that chloralose affected the central nervous of the brain; after one-hour, dogs made unsuccessful trials to move or to stand up; they stumbled in contact with all objects, showing the typical behavior of a dog after a brain intervention. [50,51,52,53] Henriot and Richet also tried the effects of chloralose on themselves, in doses up to 0.40 g. They slept very well, arose without problems, without suffering from diarrhea, dyspepsia, and all the painful effects accompanying the absorption of small doses of morphine or chloral. All these results indicated clearly that chloralose should be considered a hypnotic substance, hence they suggested their colleagues to use this compound for the treatment of neurasthenia, neuralgia, ataxia, and other brain illnesses, even diabetes. [50,51,52,53]

In other publications Henriot and Richet reported the preparation and properties of similar compounds prepared by the reaction of chloral with arabinose, xylose, galactose, and levulose. [54,57,58] Arabinose reacted with chloral in the same manner as with glucose: it formed two compounds, one soluble in water, the other, slightly soluble, which they named arabinochloralose and paraarabinochloralose, respectively. Paraarabinochloralose crystallized as needles melting at 183 ℃, was moderately soluble in cold and hot water, very soluble in hot alcohol, ether and benzene and had a rotatory power a = -23.2^0 . Henriot and Richet injected varying doses of this compound to dogs, cats, rabbits, and

guinea pigs, and observed the corresponding physiological effects. The results indicated that the lethal dose was about double that of chloralose (over 0.50 g/kg), without presenting the hyper excitation period that characterized chloralose. Xylose reacted with chloral more easily than arabinose, yielding plates melting at 132 ℃ and rotatory power a = -13.60 . The amounts of xylochloralose prepared were too small to carry physiological studies. [57]

Lipases

In previous publications Hanriot had shown that starchy food transformed almost quantitatively into fats, with release of CO_2 and without access to the corresponding oxygen. [40,43,44] Thus fat was the only reserve of a significant amount of hydrocarbon. This result led him to inquire by what means the organism absorbed the fats. It was known that fats were not attacked by sodium carbonate at the body temperature; consequently, they could not be saponified by the weak alkalinity of plasma. Perhaps, then, the blood contained ferment (enzyme) able of attacking them. Natural fats did not seem appropriate to study this possibility because they were insoluble and the resulting fatty acids were not wet (emulsified) by blood. For this reason, Hanriot searched for a fatty ester, which was sparsely soluble in water but easily emulsified, such as monobutyrin. Berthelot had already shown that monobutyrin was easily saponified by the pancreatic juice, a process easy to follow by treating the liberated acid with sodium carbonate. [59,60]

As a first step, Hanriot verified that the blood serum was able to saponify rapidly monobutyrin, as along as the solution was neutral or slightly alkaline. The acidity increased regularly with the amount of serum employed a result that allowed comparing the activity of diverse serums and thus determine their richness in the enzyme. In the following series of experiments, he verified that serum also saponified oils and natural fats, although at a slower rate. All these processes were not influenced by air. Hence, it was clear that the blood contained a ferment, which Hanriot named lipase, able to saponify the fats present in the organism. Lipase was found to be very stable and remaining in the serum for a long time (at least eight days). [60]

The next step was to search the location of the enzyme in other tissues and fluids of the organism. [61] Hanriot tested the serum of many animals, among them, a healthy man, dog, horse, cow, veal, sheep, donkey, rabbit, and guinea pig, and found lipase in all of them. He then generalized and claimed that all mammals contained lipase in their blood, although in different amounts. Analysis of the tissues indicated that in addition to blood, lipase was present only in the pancreas and the liver, and most probably it originated from the blood globules. In the case of undernourishment its role was solubilization of the fat reserves of the organism into the blood stream, to be burned at the proper location. Hence, it was necessary to distinguish between the *lipasic* action of the

blood, which did not involve saponification of the fats, and the *lipolytic* action of the same, consisting in the total oxidation of the fats into water and CO_2. [61]

Hanriot and L. Camus developed a method for the dosage of lipase. [62] In their first set of experiments they used horse blood, because it was easy to obtain in large amount and its was the most active of all the animals tested. This blood, kept aseptic in sealed tubes for two months, showed the same lipasic activity, proving its stability. The lipase was dosed by determining the amount of monobutyrin it saponified (with sodium carbonate). The pertinent experiments showed that the amount of butyrin added or the products of the reaction (glycerin and sodium butyrate) did not affect the result of the reaction. The reaction was strongly affected by the temperature. For example, at 0 ℃, the relative amounts of ester saponified after 10 and 60 min were 4.5 and 13.5, respectively; at 50 ℃ the corresponding figures were 22.6 and 71.2 (the enzyme decomposed at higher temperatures). Hanriot and Camus suggested that the activity of the enzyme be determined by titrating it at 25 ℃ with a sodium carbonate solution containing 2.12 g of the salt per liter. [62]

Hanriot also proved that the lipases of different origin (blood, pancreas, and liver) were different. [63]

Sugar in blood

Experiments conducted in 1895 showed Hanriot that the direct oxidation of fats did not originate the sugar, glycogen, or other reducing substances present in the blood. It seemed then that the oxidation process in the blood proceeded indirectly; an assumption that seemed justified by the increase in weight that took place during fasting. [64] Hanriot conducted a series of experiments to determine the mechanism of the reaction. Preliminary experiments showed, on the one hand, that a mixture of fat with platinum black or an oxidase enzyme such as laccase did not oxidize in the presence of air. On the other hand, passing a stream of ozone through neutral and purified fat resulted in considerable absorption of the gas; within 50 h 1.371 g of fat absorbed 0.312 g of ozone, corresponding to about 23 % of the primitive fat. Hanriot analyzed the product of the reaction and found that it did not contain reducing substances, sugar, starch, or cellulose. It seemed to contain fatty acids, such as acetic and butyric acids. [64]

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