

Léon Ambard (1876-1962): his priority in using urea as a tool for assessment of kidney function in healthy subjects and in patients undergoing renal surgery



Carmela Bisaccia¹, Luca S De Santo², Natale G De Santo³

1 Istituto Mazzini, Naples, Italy;

2 Chair of Heart Surgery, University of Foggia, Italy;

3 Emeritus Professor of Nephrology, Università della Campania Luigi Vanvitelli, Via Pansini 5, Nephrology, Pad. 17, 80131 Naples, Italy.

Corresponding Author: Prof. Carmela Bisaccia

Home address: Via Solimena, 169 - 80129 Naples, Italy; phone: +393357084426 ; e-mail: cbisacc@tin.it

ABSTRACT

Léon Ambard (1876-1962) was born in Marseille (France). He studied at the Sorbonne in Paris where he received his medical degree in 1905. In the years 1909-1914 he was chief of the laboratory of the Department of Urology at the Necker Hospital. His task was to find a method for assessing renal function with the goals of: 1. prognosticating the effects on the kidneys of surgical operation on the urinary tract and 2. for the early detection of renal impairment. He successfully devised the Urea Secretary Constant which was named after him (Ambard's Constant). He was able to establish the laws governing urea handling by the kidney in health and disease and attracted to the topic the most innovative physician scientists of those days including Thomas Addis and Donald Van Slyke. His findings ensured his promotion to Professor of Pharmacology at the University of Strasbourg in 1919. In 1930 he was nominated correspondent member of the National Academy of Medicine. In the same year he was promoted to professor of medicine. Ambard is credited with an impressive list of excellent papers and books including *Physiologie Normale et Pathologique des Reins* which had 3 editions (1914, 1921 and 1930). He retired in 1947 but remained very active till the end of his life (May 19, 1962). His last publication (*Ultrafiltration*) was written in English with Simone Trautmann (1961).

KEYWORDS: Léon Ambard, Urea Secretary Constant, Urea Clearance, Thomas Addis, Donal D. Van Slyke, laws of renal urea excretion

Ambard's life

Léon Ambard (Figure 1, Table 1), dit Léo Ambard, was born in Marseille in 1876. He studied at La Sorbonne in Paris from which he received his medical degree in 1905. He was assistant to Professor Edward Enriquez (1905-1911) and was called by the French urologist Félix Legueu (1863- 1939) to direct the laboratory of the Division of Urology at The Necker Hospital (1911-1914). In those years he made significant contributions to the diagnosis and prognosis of the functional renal impairment that ensues of the kidneys after surgery for urological problems, in the course of which he produced outstanding research on factors governing urea excretion by the kidneys. He wrote an important book on *Physiologie Normale et Pathologique des Reins* (Figure 2) for which Félix Legueu wrote a preface which also appeared in the subsequent editions of the book (Table 2), published in 1920 and in 1931 (Figure 2).



Figure 1 - Léo Ambard (Académie Nationale de Médecine, Paris)

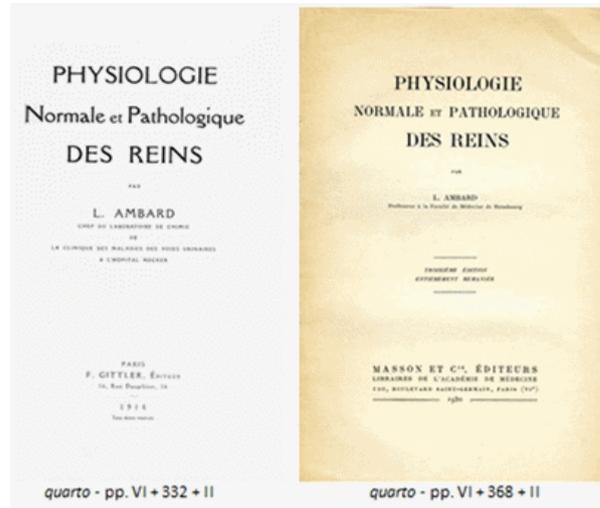


Figure 2 - Front Page of the *Physiologie Normale et Pathologique des reins*. (Académie Nationale de Médecine, Paris)

After his return from the 1st World War, to which he participated with honor, in 1919 he moved to Strasbourg as Professor of Pharmacology. On May 20 1930, he was elected National correspondent to the Académie de Médecine (Figure 3). Of 50 members of the Académie 47 voted for him. In the same year he became Professor of Medicine. He died on May 19, 1962 (1-3).

1876	Born on February 12, in Marseille
1898-1905	Studies at the Medical Faculty of la Sorbonne in Paris: External fellow in 1898, Internal fellow in 1901, MD 1905
1905-1911	Assistant to Professor Edward Enriquez (1865-1928) at la Pitié
1911-1914	Chief of the Laboratory of Urology at Necker Hospital at request of Félix Legueu
	Studies on urea excretion by the kidneys
1914	First edition of <i>Physiologie Normale et Pathologique des Reins</i>
1919	Chair of Pharmacodynamics and Experimental Medicine at the University of Strasbourg, which in 1922 was renamed as Chair of Pharmacology and Experimental Medicine
1930	Chair of Medicine B at the University of Strasbourg, as successor of Léon Blum
1930	Correspondent member of the Academy of Medicine in Paris
1939	1 st of September the University is moved into the Sanatorium of Clairvivre at Clermont-Ferrand a unique place of French Resistance
1945	1 st of October back to the Chair of Medicine B at the University of Strasbourg
1947	Retirement from the university, starts studies on ultrafiltration
1961	L. Ambard and S. Trautmann publish <i>Ultrafiltration</i>
1962	Death in Paris on May 19

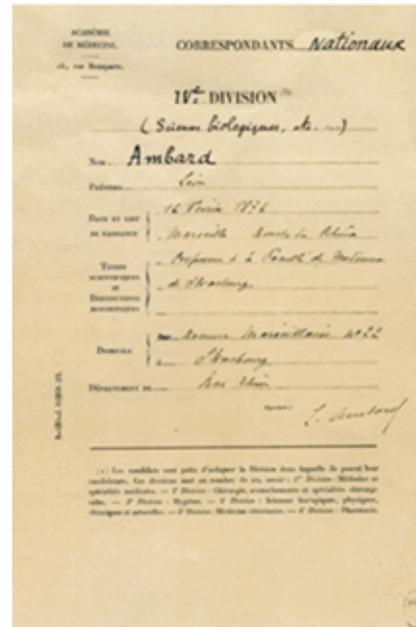


Figure 3 - Certificate of Admission to the Académie Nationale de Médecine. (Académie Nationale de Médecine, Paris)

Table 1 - Ambard's life: a synopsis

From the preface of Professor Félix Legueu

There was no need of a preface, but it gives me the privilege to attest my high esteem and the appreciation for his collaboration and to explain the reasons for which I have asked him to write this book. After Ambard took the direction of the Laboratory of the Division of Urology, works of high originality have been delivered by his brainy activity. By studying the concentration of urea in blood and urine he discovered that urea excretion occurs following precise mathematical rules and that a constant number represents this physiological ratio. From the practical point of view the excretory coefficients for urea and chloride are used for studying renal function at Necker Hospital, and represent a rigorous precise method, more accurate than any other, to understand the functional state of the kidneys. For this work Academy of Science has assigned to Mr. Ambard one of the six Montoya prizes and awards, the highest sign of distinction which in our country crowns scientific research. On my arrival at Necker I have asked Mr. Ambard to give a course on physiological and pathological function of the kidneys, two times a year for the fellows of the clinic and for those joining our group to study the complexity of the kidney function. For their interest I asked him to vulgarize those seminars for a larger audience and give him the possibility to explain his vision and ideas about normal and pathological function of the kidneys. v

January 30, 1914

Table 2 - Léo Ambard - *Physiologie normale et pathologique des reins*. F. Gittler, Paris 1914, pp.332

Timeline of building-up a critical mass of data on urea synthesis, metabolism and excretion

It took centuries to build a critical mass of data on urea synthesis, metabolism and excretion (4-6). Table 3 lists scientists who contributed to that process (7-16).

Year	Scientist/Life Span/Country	Findings
After 168AC	Galen (129-c.130-c.200/c.216 AC) Pergamon and Rome.	Excessive food intake not healthy (<i>De causis morborum</i>).
1591	Prospero Alpini (1563-1616), Republic of Venice.	First description of Mediterranean diet.
1614	Santorio Santorio (1561-1636), Republic of Venice.	Balance between food and drink intake and excreta (urine, feces, perspiration).
1773	Hilaire Rouelle (1718-1779), France.	Saponaceous extract of urine; high in nitrogen content, crystallizes into octahedral rather than cubic crystals of sea salt.
1799-1908	Antoine Fourcroy (1755-1809), France.	Urea crystallized, nitrogen content determined.
1813	John Bostock (1773-1846), UK.	First to realize the relationship between the diminution of urea in urine and its raising in blood.
1828	Friedrich Wöhler (1800-1882), Germany.	First synthesized urea, an organic substance, from silver cyanate and ammonium chloride.
1829	Robert Christison (1797-1882), UK.	Urea increased in blood and reduced urine in patients with Bright's disease.
1836	Richard Bright (1789-1858), UK.	1 st description of dropsy and proteinuria in end-stage kidney disease.
1850	Mariano Semmola (1831-1895), Kingdom of Naples.	Effects of various protein intakes on albuminuria, urinary uremia and specific gravity in Bright's Disease.
1851	Friedrich T. von Frerichs (1819-1885), Germany.	Identified stages of Bright disease through urea concentration.
1856	Joseph Picard (1834-1896), France.	Differential urea levels between renal artery and vein.
1869	Lionel Smith Beale, (1828-1906), UK.	Low protein diet in renal disease would lower urea generation.
1883	Johan Kjeldahl (1849-1900), Denmark.	Introduced an exact method for nitrogen measurement.
1902	Hermann Strauss (1864-1944), Germany.	Blood urea introduced in clinical medicine.
1904	Fernand Widal (1862-1929), France.	Relation of protein intake to blood urea in Bright's disease. Uremia.
1904	Nestor Gréhant (1838-1910), France.	First simultaneous determination of urea in blood and urine.

Table 3 - Building a critical mass of data on urea excretion by the kidneys before Ambard

Nestor Gréhan, an assistant to Claude Bernard (16), was the first to experiment on the ratio of urea concentrations in urine and blood (U/B). In the introduction of his 1904 paper (14) he writes:

"I have started the new investigation in order to allow physiologists and physicians to define exactly kidney failure and to identify when the disease begins its course. At that time it might be possible to reverse the disease and to cure it. I have gained experience with my doctoral thesis entitled *Investigations on Urea Excretion by the Kidney* (1870) and nurtured it over the years. I use nitric acid". To this end, red blood cells must be separated. To measure urea, it is necessary to prepare an alcoholic extract. This is necessary since when nitric acid reacts with urea it causes the formation of a gaseous mixture of N, NO₂ and H₂CO₃. The latter is then adsorbed on tablets potassium carbonate. With this method, Gréhan studied dogs (U/B = 124) and a sample of muscle (psoas) from a patient who died with uremia and who had passed 210 ml of urine the day before dying. The ratio of urea between urine and muscle was 10, a value well below that in dogs.

Ambard had specialized in physiology of the kidney in order to distinguish between the renal excretion of threshold and non-threshold dependent substances. For him non-threshold substances are continually excreted in urine as long as they are present in blood (urea, sulphate). Threshold substances do not appear in urine below a definite and constant blood level, that is specific for each substance. The best known threshold dependent substance, glucose, was primarily identified by Claude Bernard, who did not mention any threshold and non-threshold substances. This concept was initiated by the German Physiologist and Pharmacologist Rudolph Magnus (1873-1927) years later in his studies on chloride which is another threshold substance, but its threshold is lower than its concentration in blood. Threshold for Ambard was an entity comparable to the height of a dam. It is with his expertise in this concept that he started to experiment on urea.

Ambard, alone as well as in association with other scientists (17-45), studied dogs and young men capable to empty their bladder easily in order to evaluate the ratio between urea concentration in urine and blood. Both were measured in g/100 ml. In preliminary studies on the time course of changes of urea in blood and urine, they noticed that blood urea was at its nadir early in the morning after a night of sleep and peaked after lunch. Urinary urea excretion varied between 0.42 g/hour between 9:00 A.M. and 10:00 A.M. and 2.40 g/hour 4 hours after lunch.

Then they decided to perform experiments collecting urine for periods lasting 36 min (36 min represents 1/40 of the total number of minutes of a day) and by obtaining blood by venipuncture at an intermediate time. They studied a substance without threshold (urea) and a substance with threshold (NaCl). In dogs, urine collections were obtained through catheters and lasted 1 hour while blood was obtained after the end of urine collection. Forty ml of blood or urine were needed to measure urea by the sodium hypobromite method.

Laws regulating urea excretion by the kidneys

Analysis of generated data allowed the formulation of 3 laws governing urea and sodium chloride excretion and established the Coefficient of Urea Excretion corrected for body weight and for maximal urea excretion of 25 g/ day. For sodium chloride – having a threshold – it was possible to calculate the augmentation limit of the threshold.

The constant (K) for urea was in the range 0.06-0.081 in man and 0.03-0.034 in dogs. It was concluded that to calculate the coefficient of secretion for urea, one had to measure urea in

blood and urine and have knowledge of the urine flow rate as well as that of urea concentration. The series of outstanding publications (17-44) that followed established the laws governing urea excretion by the kidney (Figure 4).

Ambard's Laws of Kidney Function

1st. "When The kidney is secreting urea at constant concentration, the output varies directly as the square of the concentration of urea in the blood".
1 subject, water intake allowed to keep urea concentration in urine constant, measure of urine output and blood concentration.

$$\frac{U_R}{\sqrt{D}} = K$$

Ur Urea in blood (g/L)
D Urea in urine (g/24 h)
K 0.07±0.01

Urea is given in g/24 hours however its collection lasts less, usually 2 hours Corrected for body weight

Ambard's Laws of Kidney Function

2nd. "When with a constant concentration of urea in the blood, the subject excretes urea at variable concentration, the output of urea is inversely proportional to the square root of the concentration of urea in urine."

$$\frac{D}{D'} = \frac{\sqrt{C'}}{\sqrt{C}}$$

2 persons, urea constant, C is Urea (g/L) in urine

For threshold substances instead of Ur he used the excess of threshold (the factor driving excretion in urine)

$$\frac{E}{\sqrt{D} \cdot \frac{70}{BW} \cdot \frac{\sqrt{C}}{\sqrt{C'}}} = K$$

Where
E Excess over the threshold
D g/24 h in urine
W kg body weight
C g/L in urine
C' standard urine concentration isotonic with standard urine concentration of 25 g/L

Ambard's Laws of Kidney Function

3rd. "When all 3 factors , blood urea, output and concentration vary, the output of urea varies in direct proportion to the square of the blood urea, and inversely proportionally to the square root of the concentration of urea in urine".

$$\frac{U_R}{\sqrt{D} \cdot \frac{\sqrt{C}}{\sqrt{25}}} = K \quad \frac{U_R}{\sqrt{D} \cdot \frac{70}{BW} \cdot \frac{\sqrt{C}}{5}} = K$$

Ur Urea (g/L of plasma)
D Urea (g/24h in urine)
C Urea (g/L urine)
25 Standard concentration of urea in urine
K 0.07±0.01 (in normal persons)

By correcting for body weight

Figure 4 - Ambard's Laws

The destiny of the Ambard coefficient

Donald Van Slyke (1873-1971), who ultimately established the clearance concept as we know it now (46), emphasized that his studies devised to assessing the functional capacity of the kidney was based on urea excretion rate that had introduced as criterion by Ambard.

“Ambard and his collaborators (Ambard 1910, 1920), Ambard and Papin (1909), Ambard and Weill (1912), whose work has inspired many investigations including our own”.

Van Slyke et al. (46) proposed and identified 2 factors that determine urea excretion. One is represented by urea concentration in plasma, the other was identified in the urea concentration in urine. Ambard held that the excretion rate of urea increases as the square root of the blood urea concentration, i.e. doubling the blood urea quadruples its excretion rate. In the work of Van Slyke et al. (46) the first law of Ambard was confirmed. In addition, they developed a new formula which resembled that of Ambard but they claimed “far greater accuracy than that originally conceived by Ambard” [...] “If this belief is confirmed, the present work is to be regarded not as a disproof of Ambard’s, but rather as an accurate advance which has proceeded along the path opened by his researches, and which has resulted in a somewhat closer approximation to his ideal of accurate functional measurement” (46).

Marshall and Davis (47) in 1914 found that when plenty of water was given the rate of urea excretion in a normal animal was directly proportional to the concentration of urea in the blood. Working on animals and using a method described by Marshall, they showed the rate of urea excretion in normal animals was directly proportional to urea concentration in the blood, and disclosed a reduced urea excretion following dehydration (47). An approximate proportionality between blood urea concentration and rate of urea excretion was published by Pepper and Austin (48) in 1915, by Addis and Watanabe (49) in 1916 and by Addis, Barnett and Shevky (50) in 1918.

Addis and Watanabe demonstrated that the first law was perfect, but there was a problem with the second law showing variations of 10% (49). They wrote:

“The approximate constancy of the combined formula which after all is roughly approximate, is due in part to the tendency for increased urea concentration in the blood to be accompanied by increased rate of urea excretion. But in large part is to be ascribed to its mathematical construction, to more variable factors—the concentration in the urine, the volume of urine and the amount of urea in the urine occur as the square or the fourth roots of their values. Their disturbing effect on the constancy of the resultant of the formula is thus greatly reduced, while the only factor used without such modifications—the concentration in the blood—is itself the most constant quantity used”.

McLean and Selling (51) measured urea and non-protein nitrogen in urine and blood of healthy volunteer persons aged 20 to 40 years by collecting urine for 60 minutes periods. They used the Davis’ method. They found that urea excretion in normal subjects and also in nephritics was governed by the two laws of Ambard relating output to blood and urine concentration respectively. Finally they expressed great interest in the future of creatinine assessment.

“Van Hoogenhuyze, Verploegh (1905) and Shaffer (1908-1909) then have showed that the hourly elimination of creatinine throughout the day in a given individual is approximately

constant. By calculating the creatinine ratio stimulating results are obtained which indicate that creatinine may be used in those who can’t empty the bladder”.

Möller E, McIntosh JF and Van Slyke DD (52) studied urea excretion in normal adults and analyzed its relationship with urine volume. They came to the following conclusions:

“Ambard and Weill were the first to include both urea output and urine volume in attempting to quantitatively to relate urea excretion to blood content”. However the square of V is valid only for volume <2 ml, at higher volume flow rates Ambard’s formula becomes more inaccurate”.

From the historical point of view is the study of D.S. Lewis (53). That paper asked to focus attention on the paper of Lamy and Meyer (54) published in 1905. In fact Lamy and Meyer endeavored to compare the concentration of urea in the blood with the rate of excretion in urine but failed to determine the importance of the rate of blood flow and consequently did not disclose any relation between the two values. That link (53) was detected five years later by Ambard and Moreno with their laws of renal function which “under routine conditions are remarkably accurate. They are correct in principle. They allow the follow-up of renal function and the rate of progress of the disease and prognosis. Any coefficient below 0.6 or above 0.9 should be regarded as abnormal. It is depressed in mixedema, fever, hyperthyroidism, in myocardial insufficiency, raised in myxedema”.

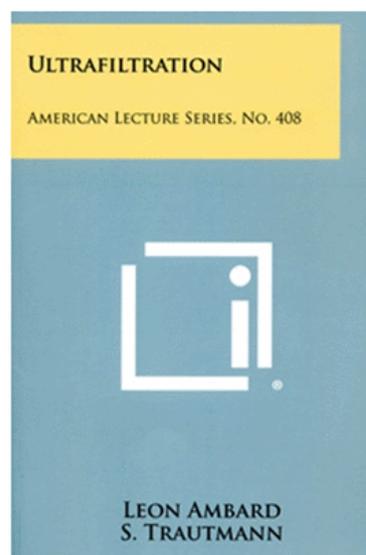


Figure 5 - Frontis of Ambard’s last book published when he was 86 year old.

Ambard a scientist with broad interests

Léo Ambard was a great investigator who every day did experiments, saw patients and wrote reports (55-60). Reference no. 56 refers to the last book co-authored by Ambard and Trautmann (Figure 5) indicating that he continued to work till the end of his life. One can say that the data and the work done before getting the chair in Strasbourg, may be considered a paradigm. He used his knowledge on threshold and non-

threshold substances in order to develop a tool capable of allowing the renal prognosis of patients undergoing surgery for urological problems. His findings were highly original and opened a new field of study. He was able to stimulate scientists from all over the world verify his findings. His experiments were repeated, discussed and of course acquired a new light. When he felt really mishandled by American Scientists, he let Donald Van Slyke know about his feelings and made it clear that all new things had a foothold in his Coefficient of Urea secretion, the “*Constante*” he had invented. Van Slyke, a great scientist magnanimously appreciated Ambard’s sadness and wrote him a letter on December 7, 1926 where he pointed out that Ambard deserved all the credit for the discovery of urea excretion (Figure 6). The letter appeared in *La Presse Médicale*.

December 7, 1926

Monsieur le Professeur Ambard
Institut de Médecine Experimentale
Faculté de Médecine
Strasbourg, France

Dear Professor Ambard:

I appreciate the situation you have described in your letter of November 15, and your sentiments in regard to it. Accordingly I am sending to the editors of *La Presse Medicale* a copy of the enclosed note, which Dr. du Moüy has kindly put into French for me. I hope that this note will assure you the honor and priority in the work on urea secretion which assuredly belong to you.

Yours sincerely,



DDV:ndly/ka/h



Figure 6 - Letter of Donald D Van Slyke concerning Ambard priority and urea clearance (Académie Nationale de Médecine, Paris)

In the obituary read before the Académie Nationale de Médecine on April 23 1963, Alexandre Marcel Monnier—member of the Academy, a famous French physiologist at La Sorbonne— reported on Ambard's sadness for the unjust attempt to delete his name from the history of clearances (3). He says that after the 1st World War, English became the language of science. So French authors were read rarely and with difficulty.

However we disagree with this sadness, for two reasons. The first is represented by the Letter of van Slyke. Not a personal letter but a letter to a very important French scientific journal. The second reason is to be found in page 94 and 95 of the 1930 Edition of *Physiologie Normale et Pathologique des Reins*. Therein we read "all French authors have given their support to the Coefficient for Urea Secretion, thus I will not cite them". The statement is followed by a list of 18 papers from abroad which

have given credit to Ambard for the discovery and are introduced by country—USA, Uruguay, Belgium, Austria, Germany, Norway, Czechoslovakia, Romania.

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