

Historical Note

Contribution of Paul Govaerts (1889–1960) to the understanding of oedema and proteinuria

The essential role of physiological knowledge in clinical medicine

Charles Toussaint

Service de Néphrologie, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

L'une des fonctions de la science clinique est de mettre à l'épreuve la validité des conceptions physiologiques.

PAUL GOVAERTS, 1953

Introduction

'Twenty-nine years ago there arrived in the small and improvised laboratory of Dana Atchley at the old Presbyterian Hospital in New York a modest but dynamic Belgian scientist and clinician armed with an inquiring mind and a small osmometer. This was Paul Govaerts.' These words were written by Robert F. Loeb on the occasion of Govaerts' retirement in 1955. On the same occasion Jean Hamburger wrote: *'A ce moment parut votre 'Fonctionnement du rein malade' [1]. Ce fut pour moi une lecture presque bouleversante. Le livre tout entier était consacré à la recherche d'explications nouvelles qui permettaient de regarder chaque syndrome morbide comme le dérèglement d'un mécanisme normal. La physiologie et la médecine du rein célébraient enfin leur union. La néphrologie moderne était née.'**

Those two quotations constitute a good introduction to the description of Paul Govaerts himself (Figure 1) and of the outstanding contributions he made to the understanding of oedema and of proteinuria. Actually, those two fields, mostly explored between 1923 and 1936, were only a part of the fertile career of this brilliant man who also undertook

extensive and fruitful investigations on water diuresis, mercurial diuresis, acute renal failure, renal threshold of glucose, and renal hypertension.

Beside his outstanding qualities of scientist and clinician, Paul Govaerts was a splendid teacher who greatly influenced countless medical students at the Université Libre de Bruxelles. His culture—not only medical—was immense and his extrovert spirit induced him to generously communicate his knowledge to others. He had an open, honest, critical and ironical mind which made him particularly feared in scientific meetings where he excelled in summing up the current stage of knowledge (or of ignorance), and therefore asking appropriate and often embarrassing questions to unwise speakers. He was also the only director of department in the hospital to question the youngest members of his staff about the financial problems they were encountering in their profession and to attempt to eventually solve them.

Oedema

In 1923 and 1924, Govaerts published [2–5] the results of his initial studies on the osmotic pressure of serum proteins in oedematous and non-oedematous subjects. In 10 normal individuals the oncotic pressure of serum protein, as measured at 18–20°C in the Cellophane membrane osmometer (Figure 2), amounted to 30–40 cm of water. If serum protein concentration is measured by refractometry, one finds that 1 g/dl protein concentration corresponds to a pressure of 4.61 cm of water. In oedematous patients, serum oncotic pressure is almost constantly below 30 cm of water, the extent of oedema being grossly proportional to the oncotic pressure decrement. In the severest cases, oncotic pressure is below 15 cm of water. Govaerts noted that the value of osmotic pressure per gram of serum protein is usually reduced in oedematous patients.

Correspondence and offprint requests to: Dr C. Toussaint, 13, avenue Mercator, 1780 Wemmel, Belgium.

*At this time your book *How the Diseased Kidney Works* appeared. This for me was almost bewildering reading. The whole book was devoted to the search for new explanations, regarding each syndrome as the disordered state of a normal mechanism. Physiology and medicine of the kidney were at last celebrating their union. Modern nephrology was born.

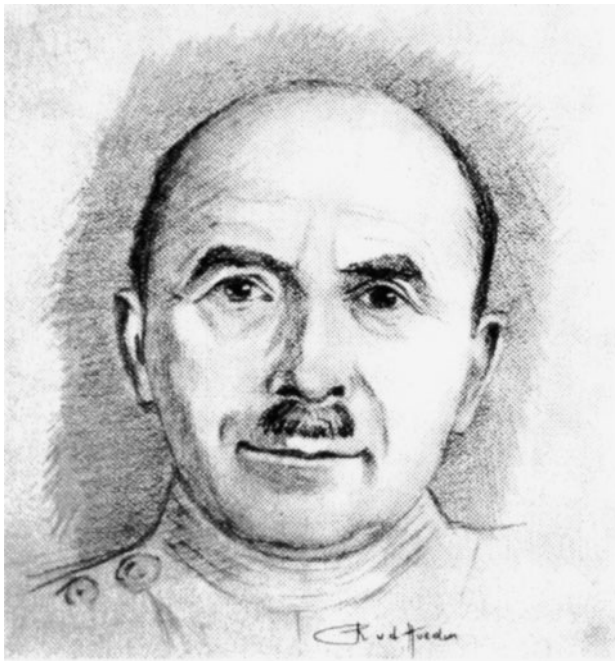


Fig. 1. Paul Govaerts in his fifties, as sketched by R. van der Hoeden MD. (*Livre Jubilaire publié en l'honneur de Paul Govaerts*, Brussels, 1955.)

The explanation of the discrepancy between oedematous and non-oedematous subjects regarding the osmotic effect of 1 g protein was found by investigating 76 individuals [6,7], and the discrepancy was found to be due to the decreased serum albumin/globulin ratio observed in most oedematous patients. Since the osmotic pressure is essentially dependent on the number of molecules by unit weight, the pressure developed by albumin is greater than in the case of globulins. Donnan's equilibrium also plays an important role in the phenomenon, the iso-electric point of albumin being far more remote from pH 7.4 than is that of globulins; the former is much more dissociated than the latter. Lower molecular weight and greater dissociation combine their effects so as to produce higher osmotic pressure in a solution of albumin than in one of globulin of equivalent concentration. In other words, the oncotic pressure developed by a given serum varies in the same direction as its albumin/globulin ratio. Indeed, if a pressure of 7.54 cm of water is attributed to 1 g/dl albumin concentration and a pressure of 1.95 cm of water to 1 g/dl globulin concentration, the values of serum oncotic pressure so calculated are in agreement with those actually measured in the osmometer with an approximation inferior to 10%. Decreased serum albumin concentration is obviously due to albuminuria in florid nephrosis, but in decompensated mitral valvulopathy, serum albumin concentration, which decreases prior to the advent of oedema, may reflect defective albumin synthesis (the site of which was unknown in 1927).

In 1928, Govaerts showed [8] that in a patient with Quincke's angioneurotic oedema, the fluid tapped

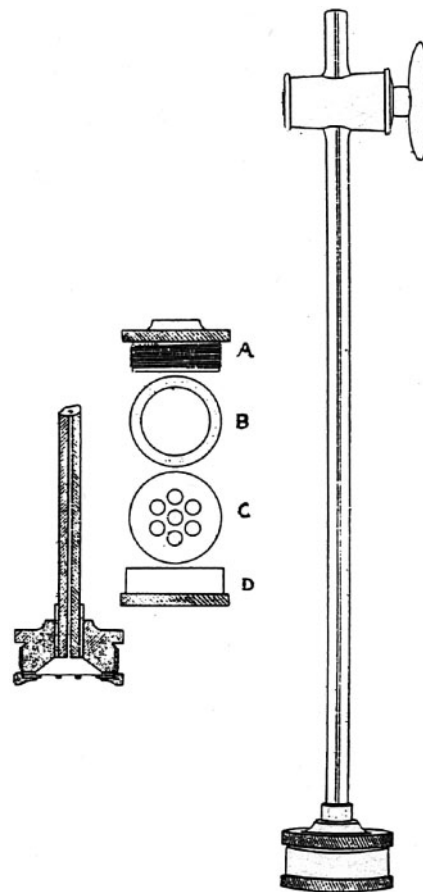


Fig. 2. The osmometer devised for clinical use by Govaerts enabled him to use much smaller aliquots of serum (1.5 ml) than those needed by former instruments. Cellophane replaces collodion as semi-permeable membrane since Cellophane is commercially available and possesses far more constant characteristics than does collodion. Built in gilt copper, the instrument includes: plate A (10 mm thick, 25 mm diameter), hollowed out in hemiconical shape; rubber ring B, exactly fitting the base of hemiconical cavity of plate A; perforated thin metal disc C with 25 mm diameter; screwed metal sleeve D to fix disc C to base of hemiconical cavity of plate A. A circular 25 mm diameter piece of Cellophane is placed on disc C, which is then firmly applied to lower opening of A by interposition of ring B. Sleeve D is then tightened, creating a small cavity, the broad base of which is closed by the Cellophane membrane supported by C. The serum sample is introduced through the upper opening of plate A, followed by a 200 mm long capillary tubing equipped with a stop-cock at its upper end and a rubber casing at its lower end. With stop-cock open, the level of serum in tubing is adjusted at 150 mm above plate A, leaving a 50-mm air-filled column between upper level of serum and the stop-cock. The latter is then closed and the osmometer is immersed in a small glass vessel containing 0.9% saline. Because of osmotic exchanges, saline penetrates into the osmometer and the level of serum rises in the capillary tubing, so compressing the air column against the closed stop-cock. Equilibrium between the osmotic and air pressures is reached before 24-h. It then remains only to measure the pressure of the air column above the serum to obtain the value of oncotic pressure of the serum aliquot. (From Govaerts [4].)

from the oedematous skin area had a protein content of 3.4 g/dl (albumin 2.4, globulins 1.0 g/dl). These findings demonstrated that this type of oedema is caused by locally increased capillary permeability, as suggested by Quincke himself.

The same year Govaerts reported [9] that the massive oedema and serous effusions observed in acute uranium nitrate intoxication in rabbits were also very rich in protein. Their fibrinogen content could be so high as to lead to spontaneous coagulation in the test tube. From those observations he concluded that the exudate induced by uranium intoxication is primarily caused by damage to capillary walls, producing the leakage of blood proteins into serous cavities and interstitial spaces. Oliguria—due to uranium nephrotoxicity—and saline administration increase the importance of oedema in intoxicated animals.

During World War II, Govaerts and Lequime [10] had the opportunity of studying 48 patients with starvation oedema in nazi-occupied Brussels. Starvation oedema, occurring in individuals having for extensive periods of time absorbed daily intakes of 25 g protein and 1300 calories, appeared as a more complex condition than previously considered. In most patients, serum oncotic pressure was below 25 cm of water and serum protein concentration was markedly decreased. In addition, basal metabolic rate was usually low and heart rate was reduced below 55/min in two-thirds of patients. Arterial blood pressure was often low but venous pressure was usually normal. The ECG showed low voltage and increased QT interval. Cardiac output was quite regularly reduced (down to 1130 ml/min in one patient) while arteriovenous difference in oxygen concentrations was markedly increased. On admission to hospital, urine output was normal but it tremendously increased after 24 h bed rest. Following the disappearance of oedema within a few days, most metabolic and circulatory parameters improved, but not to normal values. It was concluded that in starvation, the mechanisms involved in oedema formation do not differ from those acting in other kinds of transudate, since in every case, hydrostatic pressure exceeded oncotic pressure. In most patients, bed rest alone led to the disappearance of oedema, but it usually recurred when the previous levels of physical activities were resumed. Long-lasting relief could only be observed after prolonged periods of rest and of adequate protein and calorie intakes.

Thus, applying to clinical medicine the physiological principles conceived by Starling [11] at the turn of the century, Govaerts demonstrated that oedema is exclusively produced by either (i) increased venous pressure (congestive heart failure), (ii) decreased serum albumin concentration (lipoid nephrosis), or (iii) increased capillary permeability (angioneurotic oedema). In many patients, oedema could be explained by various combinations of those three factors.

Proteinuria

Around 1930 Cushny's theory of filtration–reabsorption as formulated by Rehberg [12] had not entirely supplanted the theory of secretion of

Heidenhain, Volhard, and others in the explanation of the process of urine formation [1]. In those days, numerous observers considered the massive proteinuria characteristic of lipoid nephrosis to be caused by the lipid infiltration of proximal tubule cells (hence the term 'lipoid nephrosis' then used to designate the minimal-change glomerulopathy of today). The disease was therefore eventually seen as a tubulopathy rather than a glomerulopathy.

In 1928, after microscopic examination of the kidney in a case of lipoid nephrosis, Govaerts and Cordier [13] suggested that the storage of cholesterol within proximal tubular cells could result from the reabsorption of cholesterol which with serum albumin would leak from glomeruli. In this regard, albuminuria would thereby constitute a particular case of increased capillary permeability.

In the department of histology of Brussels University, Gérard and Cordier were conducting investigations in comparative histophysiology of the kidney in vertebrates [14]. They had particularly studied the phenomenon of *athrocytosis* (reabsorption followed by storage in granular form) of various colloidal dyes by cells of the proximal tubule.

In amphibians the peritubular capillary network of the kidney is supplied by both renal artery and renal portal vein. Thus, in the toad, ligating the arteries irrigating one-half of the kidney suppresses glomerular function in this region, whereas the other half of the operated kidney, as well as the intact contralateral kidney, may be observed as controls. In this model, the intravascular injection of a highly dispersed colloidal dye, such as trypan blue, was followed by the appearance of blue granules in cells of proximal tubules corresponding to normal glomeruli, whereas tubules with functionless glomeruli were devoid of any dye [15]. This observation suggested that trypan blue must cross the glomerulus before being taken up by cells of the proximal tubule and that tubular secretion is in no way involved in the process. The objection could, however, be raised that suppression of the arterial supply might have inhibited some normal secretory mechanism, so explaining the lack of dye in the region deprived of glomerular circulation.

The latter objection was refuted by the use of salamanders by P. P. Lambert, a research student of Gérard's laboratory who, some 20 years later, would succeed Govaerts as director of the department of medicine and laboratory of experimental medicine at Brussels University. The salamander possesses two types of nephrons (Figure 3): (i) closed nephrons, similar to those of mammals, and (ii) open nephrons, with persisting nephrostomial duct, a structure connecting the initial part of proximal tubule with the peritoneal cavity. This anatomical feature enables the experimenter to introduce into the lumen of proximal tubules—*via* the peritoneum—various substances unable to cross the glomerular barrier. Injected into blood circulation, highly dispersed colloidal dyes, able to cross glomeruli, were found in equivalent amounts within tubular cells of both open and closed

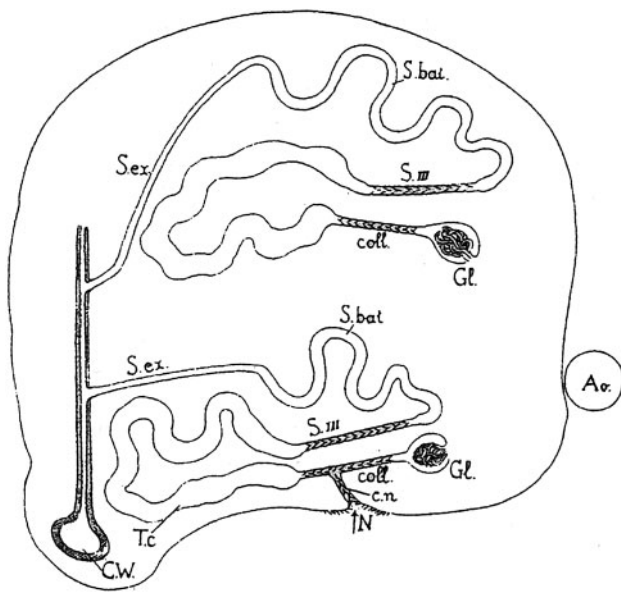


Fig. 3. Schematic transverse section of salamander kidney, showing distribution and connections of the two types of nephron. Above (dorsally), closed nephron; below (ventrally), open nephron in communication with peritoneal cavity. Ao, aorta; C. W, Wolffian duct; Gl, glomerulus; coll, ciliated neck of proximal tubule; S. III, ciliated segment III; S. bat., 'distal tubule'; S. ex., excretory segment; N, ciliated nephrostome; c. n., ciliated nephrostomial duct. (From Gérard and Cordier [18].)

nephrons. On the other hand, if such substances were administered intraperitoneally, dye granules were far more abundant in tubular cells of open nephrons than in those of closed nephrons. Finally, intraperitoneal injections of poorly dispersed dyes, which do not cross glomeruli, were followed by their exclusive storage in tubular cells of open nephrons. Thus, athrocytosis is not confined to small-size particles able to cross glomeruli, but it also involves larger particles not clearing glomeruli [16].

Furthermore, as previously observed in the open nephron of larvae of *Discoglossus* [15], athrocytosis of colloidal dyes by the proximal tubule of the salamander open nephron displays a gradient according to which athrocytosis of poorly dispersed particles occurs more distally than the process involving highly dispersed dyes [17].

Lambert also studied the handling of proteins by salamander nephrons. Subcutaneous injections of ovalbumin (MW 34 000) were followed by its storage in tubular cells of both open and closed nephrons, whereas subcutaneous administration of serum albumin (MW 68 000) produced only faint athrocytosis of protein in all nephrons. In contrast, subcutaneous injections of globulin (MW 103 000) or of casein (MW 180 000) remained negative. On the other hand, it was only after their intraperitoneal administration that globulin or casein became visible in tubular cells of open nephrons but never in those of closed nephrons. Finally, intraperitoneal injections of albumin, of globulin, or of total serum demonstrated, as

with colloidal dyes of different dispersions, a gradient of tubular permeability: the larger the molecular size of the administered protein, the more distally located its site of athrocytosis along the proximal tubule [17].

Meanwhile, returning to lipid nephrosis, Gérard and Cordier showed that in salamanders, intraperitoneal injections of high-cholesterol sera taken from lipid nephrosis patients were regularly followed by massive storage of cholesterol by tubular cells of open nephrons, so reproducing the very picture of human lipid nephrosis [18].

Thus, those well-designed experiments of histophysiology fully confirmed the hypothesis put forward by Govaerts and Cordier [13] explaining the pathogenesis of lipid nephrosis. In the book [1] so enthusiastically praised by Jean Hamburger, Govaerts could write: 'So, the mechanism involved in cholesterol overloading of tubular cells becomes obvious: actually, the essential lesion in lipid nephrosis is abnormal permeability of the glomerulus. This alteration allows the leakage of blood proteins and cholesterol to the proximal tubule, and those substances, reabsorbed by tubular cells, accumulate within their cytoplasm in the form of lipid and protein granules. The granular aspect of the tubular cells is not due to degeneration of those structures. On the contrary, it demonstrates that the tubular epithelium fulfils its function of clearing colloids leaking from diseased glomeruli. In brief, the granular state of the tubular epithelium is the consequence of increased glomerular permeability'.

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